COMMONWEALTH OF AUSTRALIA

(Patents Act 1990)

IN THE MATTER OF: Australian Patent Application 696764 (73941/94).
In the name of:
Human Genome Sciences Inc.

- and -

OPPOSITION THERETO BY:
Ludwig Institute for Cancer Research under Section 59 of the Patents Act.

STATUTORY DECLARATION

I, **John Stanley MATTICK,** Professor of Molecular Biology, and Director of the Australian Research Council's Special Research Centre for Functional and Applied Genomics, Director of the Australian Genome Research Facility, and Co-Director of the Institute for Molecular Bioscience at the University of Queensland, St Lucia, Queensland 4072, Australia, declare as follows:

1 BACKGROUND and QUALIFICATIONS

1.1 I am currently the Foundation Professor of Molecular Biology in the Department of Biochemistry at The University of Queensland, the Director of the ARC Special Research Centre for Functional and Applied Genomics, the Director of the Australian Genome Research Facility, and the Co-Director of the Institute for Molecular Bioscience at The University of Queensland in Brisbane, Australia.

1.2 The research that I have conducted over the last 28 years is presented in my curriculum vitae through my publications and presentation. Exhibited to me and marked with the letters "**JSM-1**" is a copy of my curriculum vitae, which itemises the publications and presentations of which I have been an author or co-author.

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1.3 I received my B.Sc with First Class Honours in Biochemistry from the University of Sydney in 1972, followed by a PhD in Biochemistry in 1977 from Monash University, on the topic of mitochondrial DNA replication and mutation. I then undertook postdoctoral work on the molecular biology of the fatty acid synthetase complex at the Baylor College of Medicine in Houston Texas from 1977 to 1981. My work on the architecture and function of this complex is now standard in biochemistry textbooks. I returned to Australia in early 1981 to work as a research scientist at the (then) CSIRO Division of Molecular Biology in Sydney, where I was the leader of a team responsible for the development of one of the world's first genetically engineered vaccines (against bovine footrot), for which I was awarded the 1989 Pharmacia-LKB Biotechnology Medal from the Australian Biochemical Society.

1.4 In 1988, I was appointed the Foundation Professor of Molecular Biology and Foundation Director of the Centre for Molecular Biology and Biotechnology at the University of Queensland. The Centre was subsequently made a Special Research Centre of the Australian Research Council, and in 1994 was renamed the ARC Special Research Centre for Molecular and Cellular Biology. The Centre grew rapidly and developed a strong national and international reputation for its research on the molecular biology of mammals and their diseases, including gene mapping, gene regulation, and developmental and cell biology.

1.5 In 1988, I was appointed the Director of the Australian Genome Research Facility that was established under the aegis of the Australian Government's Major National Research Facilities Program at the University of Queensland in Brisbane and at the Walter and Eliza Hall Institute for Medical Research in Melbourne.

1.6 In 2000, the Centre for Molecular and Cellular Biology amalgamated with the Centre for Drug Design and Development, and elements of other research centres, notably the Centre for Microscopy and Microanalysis and the Advanced Computational Modelling Centre, to form a new Institute for Molecular Bioscience, which is currently being constructed at the University of Queensland. I am Co-Director and Research Director of the Institute for Molecular Bioscience.

1.7 Also in 2000 I and my colleagues successfully applied for a new Special Research Centre grant from the Australian Research Council, and I now

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also hold the position of Director of the ARC Special Research Centre for Functional and Applied Genomics, within the Institute for Molecular Bioscience. This Centre and the Institute is concerned with integrated research ranging across the spectrum from genomics and genetics, developmental biology, cell biology, structural biology, and biological chemistry, all underpinned by advanced bioinformatics and computational biology.

1.8 Now exhibited to me and marked with the letters "**JSM-2**" is a summary of the research that I have conducted over the last 29 years. For ease of description I have not identified, in the summary, all of the publications that I have authored or co-authored. Instead, I have identified only those publications that I consider are my most significant. I refer to those publications by the numbers corresponding to those publications set out in my curriculum vitae.

1.9 I have been intimately involved in molecular biology since 1972. Since 1977 my research has progressively employed a range of recombinant techniques to isolate, clone and express genomic DNA and cDNAs encoding various proteins from and in a variety of different organisms including prokaryotes (bacteria), simple eukaryotes like yeast, and animal cells. Over this period I have observed either first hand or from a close distance the research that others in my field were conducting.

1.10 Since returning to Australia in 1981, I have taken a very active role in the conduct and development of molecular biology in Australia. I am a member of the Board of two other national facilities concerned with advanced molecular biology, the Australian National Genome Information Service (ANGIS) and the Australian Proteome Analysis Facility (APAF), and of several Advisory Boards of major institutions and companies active in basic and applied research in molecular biology. Details of the committees and Boards that I have been involved with over the last twenty years are provided in my curriculum vitae (JSM-1).

1.11 I have advised the Queensland State Government and the Prime Minister's Science, Engineering and Innovation Council on issues in genome science, gene technology and biotechnology, and am a member of the Queensland Bioindustries Advisory Council and a member of the Executive of BIOCOG, (Biotechnology Consultative Group) which advises the Federal Minister for Industry, Science and Resources on the

development of the biotechnology industry in Australia. I have also represented Australian molecular biology and biotechnology at senior meetings in the United States, Europe and Japan, and was involved recently in the agreement between Celera Genomics Corporation and the NHMRC, to make available Celera's human, mouse and Drosophila genome databases available to Australian biomedical researchers.

1.12 I have spent research periods in Sydney, Melbourne, Brisbane, Houston, Cambridge and Oxford, and am familiar with most molecular biological research groups in Australia. I have visited many of the major international institutions involved in molecular biology and genome research. I am a frequent guest speaker at national and international conferences in relation both to my own work and to the development of molecular biology in general. For example, I delivered the keynote addresses at the 1995 Conference of the Genetics Society of Australia and the 1996 Conference of the Australian Society for Medical Research, and an invited plenary address at the 2000 International Congress of Endocrinology. I believe this contact with the field has allowed me to become familiar with the field nationally and internationally, and with the general level of skill possessed by those working in this field in Australia.

1.13 Further, as a research scientist and the leader of an active research group, the Professor of Molecular Biology at the University of Queensland, the Director of the ARC Special Research Centre for Molecular and Cellular Biology, the Director of the ARC Special Research Centre for Functional and Applied Genomics, the Director of the Australian Genome Research Facility, and the Co-Director of the Institute for Molecular Bioscience, I have been (and am) required to have and to maintain a strong working knowledge of the Australian and international scientific literature concerning molecular biology. I have learned about molecular biology through my research training and activities, postdoctoral experience in the United States, sabbatical experience at the University of Cambridge and the University of Oxford, publications, research supervision of postdoctoral fellows and Ph.D., honours and undergraduate students, my professional involvement with numerous Australian and International organisations and industries, attendance at scientific conferences and symposia, and referee duties for various local and international journals and organisations. When I visit other research groups I often discuss with them recent developments in my field of

expertise. I would also convey relevant knowledge gained from those discussions to my research team upon my return.

2 MY INSTRUCTIONS

2.1 Human Genome Sciences Inc's (HGS') Patent Attorneys have provided me with a copy of a document entitled "*Guidelines for Expert Witnesses in Proceedings in the Federal Court of Australia.*"

2.2 HGS' Patent Attorneys have also provided me with copies of the following documents:

2.2.1 The patent specification accompanying Australian Patent Application 696764 (AU-B-73941/94) in the name of Human Genome Sciences Inc ("HGS"), entitled "Vascular Endothelial Growth Factor 2" ("the patent specification"); and

2.2.2 The Statutory Declaration of Peter Adrian Walton Rogers that was executed on 16 February 2000 ("Associate Professor Rogers' statutory declaration").

2.3 I have been asked to do the following with each of the documents identified in paragraph 2.2:

2.3.1 To review the patent specification and to describe what it would have conveyed to me had I read it in March 1994;

2.3.2 To review and provide comments on Associate Professor Rogers' statutory declaration; and

2.3.3 To base all comments presented herein on my knowledge as at 8 March 1994, unless I specifically state otherwise.

I have done this and my comments are set out in this Statutory Declaration.

2.4 Now exhibited to me and marked with the letters "**JSM-3**" is list of the documents provided to me by HGS' Patent Attorneys.

2.5 In this statutory declaration I refer to and discuss a number of documents. I am informed by the Patent Attorneys representing HGS in these proceedings that a copy of each of the documents that I discuss in this declaration will be separately filed and served in support of this opposition.

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3 THE PATENT SPECIFICATION

3.1 I am informed by the Patent Attorneys for HGS that the HGS Patent Specification AU-B-696764 has an earliest date of filing of March 8, 1994 ("the HGS priority date"), which was established by the filing of United States patent application 08/465,968 ("the priority application"). I am also informed by HGS' Patent Attorneys that subsequently a PCT application was filed on 12 May 1994 [12.05.94] ("the HGS filing date"), which claimed the benefits of the priority application. I am further informed by the patent attorneys for HGS that the PCT application was published on 25 September 1995 [25.09.95] in Australia and on 14 September 1995 [14.09.95] by the World Intellectual Property Organisation (WIPO), entered the national phase in Australia and was published as accepted on 17 September 1998 [17.09.98].

3.2 The patent specification relates to VEGF-2 polynucleotide sequences; polypeptides that are encoded by those polynucleotide sequences; uses of the polynucleotide and polypeptide sequences; means for isolating the polynucleotide sequences; and means for producing the encoded polypeptide sequence. As of March 1994 I was generally familiar with what was known and practised in the field of molecular biology in Australia and overseas and, in particular, the use of molecular biological techniques in isolating, cloning and expressing protein, although I was not specifically working with the PDGF/VEGF gene family.

3.3 HGS' Patent Attorneys have informed me that VEGF-2 and VEGF-C are the same molecule. The fact that VEGF-2 is now known by another name does not cause me any difficulty in understanding the information in the patent specification. When a new protein is identified it is usually named by the first group or groups to discover it, unless there is a precedent concerning the naming of the new protein because of its relationship to others (i.e. it belongs to a family members which has been described previously).

3.4 Before discussing the information provided in the patent specification I have been asked to comment on (a) the environment in which molecular biologists operated in 1994 in Australia, and (b) the field of gene cloning and protein expression as at 1994.

(a) The Field of Molecular Biology in Australia in 1994.

3.5 By 1994 many laboratories in Australia were using molecular biological techniques. These included virtually every department of biochemistry, microbiology and genetics in the different universities around Australia, many research organisations and institutes such as the CSIRO, the Walter and Eliza Hall Institute of Medical Research, the Queensland Institute of Medical Research, the Garvan Institute of Medical Research (among many others) and companies such as Biotech Australia Pty. Ltd. and Commonwealth Serum Laboratories Ltd. I was generally aware of this by reason of my own work and experience. I routinely met with other scientists from other laboratories and institutes during visits to those places and during conferences during which we would discuss both research findings and methodologies. I also supervised and maintained contact with graduate and postdoctoral students whom I supervised and worked with or who had been in the laboratories in which I have worked. Information and knowledge gained from those discussions would be conveyed by me to my research team.

3.6 The normal working group in a laboratory using molecular biological techniques would consist of an experienced Ph.D. graduate (a research scientist or academic staff member) advising more junior Ph.D. graduates (postdoctoral fellows or research officers) and/or research assistants and/or graduates and/or Ph.D. students. In my experience, a person of ordinary skill in my field of technology was and is someone who has the necessary skills to perform a particular task, rather than a person simply with a certain level of academic qualification. Moreover such a person is someone who is capable of designing and carrying out experiments with a minimum degree of supervision. People with a basic degree, working as research assistants, would often be taught in a short period of time how to use molecular biological techniques in a professional manner and would thereafter become the researcher(s) who conducted the research at the laboratory bench. Sometimes that work would be under the strict direction of a person with a Ph.D and other times it would be at their own initiative, subject to general direction, depending on the abilities of that researcher.

3.7 Generally, one of the avenues by which I and other scientists in Australia keep up-to-date with developments in our field is through reading research (journal) articles. There are a number of journals that are, and

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were before 1994, commonly read by most biological scientists, some of those publications included *Nature*, *Science*, *Proceedings of the National Academy of Science (USA)*, and *Cell*. After that a researcher would tend to specialise in what they read, taking the best papers from journals that are specific for their area of interest.

3.8 Scientists in Australia, as do scientists elsewhere, also constantly observe what is happening overseas through international conferences and international contacts. Before 1994 and now, there were (are) a lot of international conferences which Australian scientists frequently attended.

3.9 In the field of molecular biology, in the mid-1990's and today, the background knowledge of researchers in Australia was the same as or similar to that of a researcher in the USA, UK, Europe, Japan and elsewhere. It could be that in the laboratories in the USA people might have heard things on the grapevine before they were published, which might not have been the situation quite so often in Australia. But apart from that, there is and was very little difference - it is and was very much an international community of scientists.

3.10 Before March 1994 (and today) many Australian scientists who did a Ph.D. in the field of molecular biology would go overseas to do post-doctoral studies. The great value in this is that these scientists get to know personally a set of people that are about the same age and at about the same stage of development, as well as more senior people. They usually keep in touch with such people throughout their professional life, and so set up information networks that develop with the years. Furthermore, such interactions as well as those at international conferences regularly lead to reciprocal visits to other laboratories.

3.11 There is little difference in the level of skill between Australian researchers in the field of molecular biology and researchers in other industrialised countries around the world. A lot of world-class work has been done in Australia and that is reflected in many publications that have come from Australia. For example, work carried out in my research centres, some of which I was directly involved with, has been published in *Nature Genetics*, *Cell*, and the *Proceedings of the National Academy of Science (USA)* - which are regarded as three of the top journals in the field. The amount of work to have come out of Australia is quantitatively

lower than that from other countries such as the United States and United Kingdom, because the number of people involved is lower, but the per capita publication rate and overall quality of the work carried out in Australia over the past three decades has been similar to that of other advanced countries, and in my opinion has been, for the most part, first rate. I believe that the work of our group is just one example that shows that Australian scientists in the field of molecular biology were often and still are the leaders in the field.

(b) Gene cloning and protein expression

3.12 By 1994 the field of gene isolation, cloning and protein expression in Australia was comparable to that in any other industrialised nation. Rapid advances in molecular engineering techniques and in particular gene amplification techniques provided researchers with a versatile set of techniques and tools for isolating and amplifying genomic sequences.

3.13 An important difficulty that researchers faced in 1994 (and still face today) is the process of determining what a new gene encodes. This involves careful consideration and scientific training, and it is not a simple or straightforward process. Importantly, the isolation of a DNA sequence does not guarantee sufficient information to establish whether the sequence encodes a protein or if it does, the nature and function of the protein it might encode. Such information had to be determined in 1994 (as it is today) by a researcher using scientific skill, their experience, their knowledge and often a wide range of different analytical and experimental tools.

3.14 However, once a DNA sequence had been cloned, further manipulations of that sequence would be relatively routine practice. Moreover once a protein sequence had been identified there were many routine methods available for analysing that protein. Computational analysis provided one method, however there were other methods, which relied on more direct experimental analysis. Researchers often used a combination of these methods to characterise a newly discovered protein. For example, by 1994 researchers were well acquainted with the fact that hydrophobic/hydrophilic characterisation and/or identification of conserved features of an amino acid sequence can indicate likely structural or functional characteristics. However, they were also well aware that such analytical tools had their limits.

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3.15 Where a researcher thought an identified protein might contain a secretion signal sequence they often searched the sequence for amino acid motifs characteristic of such a sequence. Computer analysis programs available in 1994 for examining proteins for secretion signal or leader sequences included P SORT and SIGNAL P.

3.16 Once the gene sequence encoding a protein had been identified, researchers could apply well-established molecular biology techniques to produce the protein in any desirable form. Expression of a known gene was a relatively routine and standard laboratory activity by 1994, *albeit* one that required care and attention. Expression of a known gene sequence involved: (a) selection (*a priori* or by trial and error) of an appropriate host-vector expression system that produced the protein in a form that would meet the end user's requirements; (b) insertion of the gene sequence into the selected vector(s); (c) introduction of the vector(s) into an appropriate host cell(s); (d) cultivation of the host cell; and (e) recovery of the expressed protein.

3.17 By 1994, when researchers were selecting expression strategies they would typically take into consideration such factors as their experience, the type of protein to be expressed, morphological and physical features of the protein (e.g. whether the protein contained a signal or leader sequence), the physiological activity of the protein and the use to which that protein was to be put.

3.18 In conducting expression experiments it was not uncommon or unusual (nor is it uncommon or unusual today) for researchers to encounter obstacles. Many such obstacles can and could be overcome by the application of ordinary skill. An example would be where the researcher was working on expression of a protein and found that the protein was not released from the cell. There are a number of reasons why this problem might have arisen and I would expect that a person of ordinary skill in molecular biology would be aware of those reasons. An obvious possibility would be that the signal sequence, necessary for the secretion of the protein from the cell, was missing or faulty. This could be remedied by adding a heterologous signal sequence as is and was routinely done. Researchers often accommodated such situations by considering and trialing a series of different expression strategies and systems. In this respect, my team and I usually assess a bank of

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different expression strategies and systems simultaneously, or at least in close sequence, when expressing a protein for the first time.

3.19 There were in 1994 many expression vectors that were commercially available or could be obtained from the author of the publication in which they were reported. Biotechnology company catalogues describing expression vectors and associated host cells in which they could be used were part of every researcher's standard operating texts and invariably contained all the essential information that a researcher required to express a particular protein. These catalogues regularly contained additional information about the system including a reference to one or more seminal papers that described the expression vector, examples of other papers where the vectors had been successfully used and information about how to purchase the vectors and their hosts.

(c) The patent specification

3.20 The patent specification relates generally to VEGF-2 polynucleotide and polypeptide sequences and provides such sequences for diagnostic, therapeutic and prophylactic use.

3.21 On page 3 (lines 30 to 32) the patent specification states:

> "In accordance with one aspect of the present invention, there is provided a novel mature polypeptide which is a VEGF-2 as well as fragments, analogues and derivatives thereof."

3.22 The information provided in Figure 1 in the patent specification discloses a VEGF-2 sequence that is 350 amino acid residues in length. For the reasons mentioned in paragraph 4.7 below, the nucleotide sequence disclosed in Figure 1 may also be read to encode an additional 23 amino acids.

3.23 After identifying the invention so far as it relates to VEGF-2 polypeptides the patent specification states on page 4, lines 1 to 3:

> "In accordance with another aspect of the present invention, there is provided polynucleotides (DNA and RNA) which encode such polypeptides."

3.24 The information provided in Figure 1 in the patent specification discloses a VEGF-2 polynucleotide sequence that is 1525 base pairs in length.

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3.25 After identifying VEGF-2 polypeptides and polynucleotides, the patent specification describes uses of those sequences. The patent specification states that the sequences can be used for therapeutic purposes such as would healing, to promote growth of damaged bone and tissue, to promote endothelialization of damaged tissues as well as diagnostics for tumours, cancer therapy, to produce antibodies against VEGF-2 and to produce or identify antagonists and inhibitors that may be used to inhibit the action of VEGF-2 to, for example, prevent tumour angiogenesis or prevent tumour neovascularisation.

3.26 On page 5 (lines 13 to 18), the patent specification refers to a deposited sequence i.e. ATCC Accession No. 75698 (plasmid 182,618) on 4 March 1994. I note that the specific details that identify the deposited clone have been written into the patent specification by hand. I am informed by the Patent Attorneys representing HGS that appropriate procedures were followed to introduce this information into the patent specification and that I am to consider the hand written information as part of the specification. I am proceeding on that understanding.

3.27 After identifying the deposit sequence the patent specification provides information about the tissue source from which the identified VEGF-2 coding sequences could be isolated. This information provides a source from which a VEGF-2 clone could be isolated and expressed. The patent specification also provides additional information about alternate tissue sources in Figure 5. Figure 5 depicts the results of northern blot analysis of VEGF-2 in a range of human adult tissues. The information contained in Figure 5 is discussed in more detail below.

3.28 On page 5 lines 24 and 25 of the patent specification, HGS identify their VEGF-2 protein as being structurally related to the PDGF/VEGF family. When comparing their protein against other PDGF/VEGF family members they observed that the VEGF-2 sequence that they identified contains a fourteen amino acid signature motif that is common to the PDGF/VEGF family of growth factors, as well as eight cysteine residues that are conserved amongst VEGF, PDGFα and PDGFβ family members. Further, they also observed that VEGF-2 shares some sequence identity with each of these family members, that identity being VEGF (30%), PDGFα (23%) and PDGFβ (22%). Figure 3 presents a comparison of the percentage homology between VEGF-2, VEGF, PDGFα and PDGFβ.

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3.29 After providing a brief characterisation of VEGF-2, HGS provides information concerning production of a recombinant product with one or more of the biological properties of VEGF-2. For example, they describe methods for constructing a large range of expression vectors and expression systems suitable for use in a range of prokaryotic and eukaryotic host cells (see e.g. pages 10 to 15 of the patent specification). They describe host cells for expression, including mammalian cells, yeast cells, insect cells, and procaryotic cells (see e.g. pages 10 to 15 of the patent specification) and the use of heterologous signal sequences to achieve efficient secretion (see e.g., page 14, lines 6-23). By March 1994 all of these techniques were routinely available from standard texts, and the indicated combinations and variations were commonly employed by those skilled in the art.

3.30 The patent specification then describes examples of diagnostic and therapeutic uses to which VEGF-2 products may be put.

3.31 Therefore, in summary, in my opinion the patent specification provides, *inter alia*, the following:

3.31.1 DNA sequences encoding VEGF-2 amino acid sequences and fragments thereof;

3.31.2 Cell sources for the identification and isolation of VEGF-2 coding sequences;

3.31.3 Methods for producing recombinant VEGF-2 in eukaryotic and prokaryotic host cells;

3.31.4 Methods for producing abundant amounts of a polypeptide isolated from recombinant cells having the *in vivo* activity of VEGF-2;

3.31.5 Methods for producing antibodies against VEGF-2 polypeptides for the purification of VEGF-2;

3.31.6 Uses of VEGF-2 for stimulating angiogenesis;

3.31.7 Uses of VEGF-2 polypeptides for stimulating wound healing and for vascular tissue repair;

3.31.8 Antagonists to inhibit VEGF-2 activity and anti-sense constructs to inhibit VEGF-2 expression;

3.31.9 Agonists against VEGF-2 polypeptides;

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3.31.10 Diagnostic methods for identifying mutations in the VEGF-2 coding sequence and alterations in the concentration of VEGF-2 protein in a sample derived from a host.

3.31.11 A method to test for *in vitro* biological function or activity of VEGF-2;

3.31.12 Pharmaceutical carriers and delivery systems for the VEGF-2 polypeptide as well as means for gene therapy to provide therapeutic and prophylactic effects against a wide range of different disease states;

3.31.13 Uses of the VEGF-2 polypeptide and gene sequence for the treatment of disease related medical conditions such as myocardial infarction (heart attacks) and ischemia; and

3.31.14 Uses of the VEGF-2 polypeptide and gene sequence for the treatment of non-disease related medical conditions such as burns, injuries and plastic surgery.

3.32 A more detailed but non-exhaustive list of the information that is disclosed in the HGS patent specification is provided in Table 1. Now exhibited to me and marked with the letters "**JSM-4**" is Table 1.

3.33 In my opinion, the disclosed VEGF-2 DNA and amino acid sequence information, the disclosed cell sources for isolating additional VEGF-2 clones, and the description for cloning and expressing VEGF-2 provide all of the information that I would have needed to express a biologically active VEGF-2 using routine scientific application. All of this information is provided in the patent specification. Indeed, without this information not only would I not have been able to identify and isolate VEGF-2 and VEGF-2 coding sequences in March 1994, I would not have known that the protein existed.

3.34 Further, the identified sequence information provided in the patent specification would have allowed me and I believe any person of ordinary skill in the field of molecular biology in 1994 to design specific strategies to obtain any polynucleotide sequence (ie gDNA, mRNA or cDNA) encoding VEGF-2. For example, the sequence information could have been used to design highly specific DNA primers that exactly match the VEGF-2 sequence, thus enabling the isolation of gDNA or cDNA VEGF-2 clones from suitable libraries or from the tissue sources identified in the patent specification.

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4 Associate Professor Rogers' Statutory Declaration

4.1 I have been asked to read and comment on the Statutory Declaration by Associate Professor Rogers. I have done this and make the following comments concerning that declaration.

General comments

4.2 Associate Professor Rogers' statutory declaration raises a number of general issues concerning the patent specification. In the following passages I will address those issues and then turn my attention to some of the specific comments that he makes.

(a) Expression of the VEGF-2 sequence

4.3 The first issue that Associate Professor Rogers puts forward is that expression of the VEGF-2 sequence would have been problematic based on the information in the patent specification because the full length VEGF-2 sequence is not disclosed in the specification and the patent specification suggests that the first 24 amino acids of the disclosed sequence may represent a secretion signal sequence. I do not agree with his perspective. I believe that a person of ordinary skill in the field of molecular biology would have been able to deal with these issues easily by applying routine trial and experimentation to produce the VEGF-2 protein, had they been presented with the information in the patent specification.

4.4 It would have been a reasonable proposition in 1994 to suggest that the first 24 amino acids might be an atypical signal sequence. I note that Dr Alitalio and his research team appeared to draw a similar conclusion in 1996 in their publication reporting VEGF-C (see: Joukov *et al.*, (1996), *EMBO Journal* 15: 290-298).

4.5 Had I attempted to express the VEGF-2 protein using the putative secretion signal sequence identified in the patent specification and had that not worked, I and I believe any other person of ordinary skill in the field of molecular biology would have considered two obvious solutions to produce VEGF-2.

4.6 First, I would have gone back to look more closely at the putative signal sequence and would have noted that it deviates in some respects from typical signal sequences. To overcome this I would have used a

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heterologous signal sequence as is and was routine in the field of molecular biology in 1994, and which is taught in the patent specification on page 7 (lines 21 to 34), page 8 (lines 1 to 4), pages 9 to 10 (lines 34 to 5), and page 14 (lines 17 to 23).

4.7 Second, I would have considered whether the signal sequence was incorrect or incomplete. In considering this issue I would have gone back and read the specification more carefully and would have noted that the specification is not entirely clear about the existence of the signal sequence. In particular, I would have observed that the specification states on page 5 (lines 25 to 28), that the first 24 amino acids are only likely to represent a signal sequence. I would have also noted that the sequence in Figure 1 possibly encoded a further 23 continuous amino acids upstream of the suggested methionine start codon. Thus, I would have looked in an appropriate cDNA library for larger VEGF-2 clones that might encode more sequence information and a *bona fide* signal sequence. In this respect I note that in Figure 5, a 2.2 kb mRNA species was detected, which I would expect to encode the full length sequence of VEGF-2 (the full length VEGF-2 sequence is now known to be transcribed as a 2.1 kb mRNA species). Any experimentation required to identify potential upstream sequences from the VEGF-2 mRNA species would be routine.

4.8 Taking into account the existence of the additional 23 amino acids at the N-terminal end of the VEGF-2 sequence disclosed in the patent specification, I would also have stitched a signal secretion sequence to the beginning of the cDNA disclosed in the patent specification, as is taught in the patent specification. I note that such an experiment was done and is described in Australian Patent Application 60467/96 (714,484) (HGS' second VEGF-2 patent application) and the resultant product from those experiments is reported to be biologically active (see page 42, line 32 to page 43 line 25 and Figures 8 and 9 -- HGS' second VEGF-2 patent application).

4.9 The patent specification describes the use of such heterologous signal sequences on page 7 (lines 21 to 34), page 8 (lines 1 to 4), pages 9 to 10 (lines 34 to 5), and page 14 (lines 17 to 23). On these pages reference is made to combining the mature sequence with a leader (secretion) sequence. Using such a system I would have been confident that I could

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have produced a secreted form of the VEGF-2 amino acid sequence disclosed in the patent specification.

4.10 In addition to the above experiments I might also have attempted to express the 350 amino acid form of the protein, and or other fragments of VEGF-2 as taught in the patent specification. Such experiments could all have been performed in parallel with routine ease. By 1994 there were a large range of methods available to researchers for doing this type of work. Furthermore, systems for carrying out such research were well established and routinely available.

4.11 I believe either of these two approaches would have produced the desired outcome of producing VEGF-2, which I note has subsequently been shown to be the case.

4.12 I have been asked to consider and comment on US patent 6,130,071 entitled "Vascular Endothelial Growth Factor C (VEGFC) ΔCYS_{156} Protein and gene, and uses thereof". This patent describes, amongst other things, the expression of VEGF-C fragments using methodologies consistent with the strategy proposed above and which were routinely available and followed in protein expression laboratories prior to 1994. In particular, a heterologous secretion signal sequence was used to express and produce biologically functional or active fragments of VEGF-C. Accordingly I believe the same principles and strategy would apply and that the results in that patent reinforce that VEGF-2 sequences may be produced using the strategy that discussed to produce a biological function or activity VEGF-2 protein.

4.13 Therefore in my opinion, the fact that the signal sequence information was incomplete would not have presented me with a formidable or even significant problem, given that the patent specification provides that a heterologous signal sequence may be used to achieve efficient secretion, and it would have involved routine experimentation to do so. I believe that by applying the information in the patent specification and a reasonable amount of routine trial and experimentation using standard protein expression and secretion techniques I could have easily produced a secreted VEGF-2 protein.

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(b) Biological assay

4.14 Associate Professor Rogers asserts that the patent specification fails to provide an assay to test for VEGF-2 biological function or activity.

4.15 I note that on page 18 (lines 6 to 8) HGS refer to a use of VEGF-2 for the *in vitro* expansion of vascular endothelial cells. I would understand from reading that passage that an expected activity of VEGF-2 is to promote growth of vascular endothelial cells in culture. I could use such an activity to verify the production of VEGF-2 as taught by the patent specification and I note that such an activity has subsequently been shown to be something possessed by VEGF-2. I refer to HGS Patent Application 60467/96 (714,484), which shows that VEGF-2 exhibits proliferative effects on vascular endothelial cells (see page 42, line 32 to page 43 line 25 and Figures 8 and 9).

4.16 In addition, had I wanted to examine a secreted VEGF-2 protein using other assays relevant for activities specified in the patent specification (see below) I would have identified someone working in the vascular biology or endothelial biology field and I would have asked them for advice about the types of angiogenic assays that were available in 1994 and how to set up the assays, or I would have asked whether they would be prepared to collaborate with me in my research by testing the protein that I had produced. By 1994 it was common and routine in Australia for researchers to collaborate on projects. Alternatively, I could have done a basic Medline search for assays that tested for angiogenic activity since the patent specification tells me that VEGF-2 is an angiogenic molecule (see page 1, 4 and 16 to 18 of the patent specification). I would then have read those papers and I would have set up appropriate assays. Among the publications that I would have located here are some examples:

4.16.1 Passaniti A, et al. (1992) "A simple, quantitative method for assessing angiogenesis and antiangiogenic agents using reconstituted basement membrane, heparin, and fibroblast growth factor." *Lab. Invest.* 67:519-528

4.16.2 Splawinski J, Michna M, Palczak R, Konturek S, Splawinska B (1988) "Angiogenesis: quantitative

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assessment by the chick chorioallantoic membrane assay." *Methods Find. Exp. Clin. Pharmacol.* 10:221-226

4.17 Therefore, I disagree that the patent specification does not provide sufficient information to undertake a biological assay for VEGF-2.

(b) Biological activity

4.18 Associate Professor Rogers asserts that the patent specification fails to demonstrate a biological activity of VEGF-2 (see, for example, paragraph 4.6.2 in Associate Professor Rogers Statutory Declaration). The patent specification provides extensive guidance for the *in vitro* and *in vivo* biological activities and uses for VEGF-2. Further the patent specification provides in Example 1 Northern Blot data (see figure 4) showing that VEGF-2 is over-expressed in breast cancer cell lines. This result indicates to me that VEGF-2 is biologically active in tumours.

4.19 According to the patent specification, VEGF-2 is a molecule that is capable of re-vascularizing damaged tissue and/or has angiogenic properties (see page 16 lines 27 to 29 of the patent specification).

4.20 On page 4 of the patent specification, HGS state that the present invention concerns a protein that possesses angiogenic behaviour (see, for example, page 4 lines 7 to 14 and lines 18 to 21).

4.21 On pages 16 to 24, the patent specification discloses a multitude of biological applications for the protein. In particular, it discloses:

(a) *in vivo* uses of the proteins such as in wound healing or re-vascularizing damaged tissue (see page 16 line 27 to page 17 line 28);

(b) *in vitro* uses of the protein, such as for the generation of inhibitors of angiogenesis and neovascularization (see page 17 line 29 to page 18 line 5) and for *in vitro* culturing of vascular endothelial cells (see page 18 lines 6 to 8); and

(c) immunological uses of the protein, as diagnostics to detect the presence of tumours in certain individuals (see page 24 lines 5 to 9) or as antagonists to treat tumours or inflammation caused by increased vascular permeability (see page 24, lines 2 to 4).

4.22 The patent specification is not restricted to the above uses of VEGF-2 proteins. It also discloses uses of VEGF-2 polynucleotides as well as uses of truncated VEGF-2 proteins. Uses of the polynucleotide sequences disclosed in the patent specification include:

4.22.1 As probes and or primers (see page 8 and Example 2).

4.22.2 In gene therapy -- Including both *ex vivo* and *in vivo* applications (see page 18 (lines 9 to 34)).

4.22.3 To identify the chromosomal location of the genomic sequence encoding VEGF-2 (see page 20 and 21).

4.22.4 For the determination of genetic diseases associated with VEGF-2 (see page 20 and 21).

4.22.5 For *in vivo* inhibition of VEGF-2 by the use of antisense technology.

4.23 On page 24 (lines 25 to 31) the patent specification identifies uses of truncated versions of VEGF-2 for inactivating the activity of endogenous VEGF-2. It also discloses how such truncated molecules may be used therapeutically as anti-cancer drugs, to prevent inflammation or to treat solid tumour growth, diabetic retinopathy, psoriasis and rheumatoid arthritis (page 25 lines 4 to 13).

4.24 Therefore, in my opinion the patent specification discloses a comprehensive range of uses of both the polynucleotide and polypeptide sequences of the invention. Such information constitutes the basic information that I would have required in 1994 to use VEGF-2 in a wide range of biological activities.

(d) The claims in the patent specification do not encompass VEGF, PDGF and PlGF

4.25 I note that Associate Professor Rogers suggests that the claims in the patent specification could *in extremis* cover molecules like VEGF, PDGFα, PDGFβ and PlGF because they include the words "fragments, analogues and/or derivatives". I do not agree with his position. In my opinion Associate Professor Rogers' comments concerning this issue are spurious and would not reflect the reasonable view of anyone experienced in the field of molecular biology.

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4.26 I would expect VEGF-2 fragments, analogues and derivatives to have greater structural similarity to VEGF-2 than other related proteins such as VEGF and PDGF, which exist as distinct proteins in nature.

4.27 Having regard to the information provided in the patent specification I note that HGS clearly distinguishes VEGF-2 from VEGF, PDGFα and PDGFβ. Figure 2 provides a comparison of the amino acid sequence of VEGF-2 and other members of the PDGF/VEGF family, which demonstrates the low level of homology between these proteins. Figure 3 presents a comparison of the percentage homology between these molecules. Using this information I could and would distinguish VEGF-2 fragments, analogues and/or derivatives from VEGF, PDGFα or PDGFβ.

(e) Hybridisation with VEGF-2

4.28 Associate Professor Rogers asserts in his Statutory Declaration that:

> "...the claim limitations directed to polynucleotide hybridization do not serve to distinguish the prior art that discloses VEGF, PlGF, or PDGF polynucleotides and/or polypeptides, because any DNA can hybridize to VEGF-2 DNA if the hybridization conditions (*e.g.*, temperature and ionic strength) are sufficiently relaxed. Neither the claims nor the specification require a level of hybridization stringency that would exclude VEGF, PlGF, or PDGF polynucleotides or encoded polypeptides from the scope of the claims. (No minimum level of hybridization stringency is required at all.)"

4.29 The claims in the patent specification refer to hybridization with a VEGF-2 polynucleotide sequence. When I read such language in combination with the description of hybridization set forth in the patent specification I would understand it to mean that hybridization conditions should be sufficiently specific to exclude known non-VEGF-2 sequences.

4.30 The patent specification provides examples (see Example 1) of hybridization conditions that could be used to specifically identify VEGF-2 sequences. Further the patent specification states that there is no detectable homology at the nucleotide level between VEGF-2 and VEGF and PDGF. By 1994 it would have been routine for me and I believe any other researcher in the field to use the hybridization conditions put forth in the specification such that there would be no cross hybridization with VEGF, PlGF, or PDGF. In this respect I refer to paragraph 2.4.3 in Associate Professor Rogers' Statutory Declaration where he indicates

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that scientists could, prior to 1994, exercise considerable control over the stringency of hybridization conditions. I would agree with this statement.

(f) VEGF 2 antibodies

4.31 Between pages 22 and 24 of the patent specification there is a description of methods for making antibodies to VEGF-2. Those methods were well known in the scientific literature and easy to perform in 1994.

4.32 In Sections 2 and 3 of Associate Professor Rogers' Statutory Declaration he repeatedly asserts that antibodies that bind to conserved regions of VEGF-2 would cross-react, to some extent, with the similar regions in VEGF or PDGF or PIGF. For example, in paragraph 2.5 he states:

> "From the theoretical universe of all possible antibodies that bind to VEGF-2, a molecular biologist with common general knowledge would reasonably expect that some antibodies which bind to these conserved regions (epitopes) of VEGF-2 would cross-react, to some extent, with the similar regions in VEGF or PDGF or PIGF. In other words, VEGF, PDGF, and PIGF are polypeptides which bind an antibody that binds (or is capable of binding) to VEGF-2. The expected antibody cross-reactivity means that the claim limitation relating to antibody binding does not exclude prior art VEGF or PDGF or PIGF polynucleotides and polypeptides from the scope of claims."

4.33 Associate Professor Rogers' comments are, in my opinion, extremely speculative. The fact that there is some sequence homology between VEGF-2 and VEGF and other proteins does not mean that there is a high probability that antibodies to VEGF-2 will cross react with VEGF or those other proteins. Antibodies generally have exquisite specificity and will only cross react with closely related proteins. I do not believe that any conclusion can be drawn about cross-reactive antibodies at a theoretical or practical level.

4.34 Further, I note that Associate Professor Rogers asserts that claim 49 includes within its scope antibodies raised against VEGF, PDGF or PIGF polypeptides. In particular he states: "... such antibodies are explicitly disclosed or suggested in...". None of the prior art documents cited by Associate Professor Rogers establish that the described antibodies bind VEGF-2. In my opinion, no conclusion can be reached about the cross-reactivity of these antibodies based on the disclosures in these publications.

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Specific Comments

4.35 In this section I address some of the more specific comments that Associate Professor Rogers makes in his statutory declaration. My decision not to address each and every paragraph in that declaration should not be taken as acceptance of the paragraphs to which I do not refer.

Paragraph 2.2.2

4.36 In paragraph 2.2.2 Associate Professor Rogers states:

> "A substantial number of amino acid changes are required to change the VEGF-2 sequence into, *e.g.* the VEGF or PDGF sequences shown in Fig. 2A-2B. However, I find no limitation in the specification or the claims setting a maximum number of modifications that may be performed to generate a "fragment, analogue, or derivative" within the scope of the claim. Thus, polypeptide and polynucleotide claims which recite "fragment," or "analogue," or "derivative" effectively encompass prior art polypeptides and polynucleotides, including but not limited to VEGF, PlGF, and PDGFα and PDGFβ polypeptides and polynucleotides."

4.37 I would not require the patent specification to set a maximum limit of modifications that can be made to a protein before I could reasonably ascertain whether a protein was a fragment, analogue and/or derivative of VEGF-2. In this respect I refer to my comments in paragraph 4.25 to 4.27. As soon as a protein starts to look more like VEGF, PDGFα, PDGFβ, or PlGF, it would not, in my opinion, be a fragment, analogue and/or derivative of VEGF-2. Thus, I would not regard any of VEGF, PlGF, PDGFα or PDGFβ to be VEGF-2 fragments, analogues and/or derivatives.

Paragraph 2.4

4.38 In paragraph 2.4 Associate Professor Rogers states:

> "Some of the claims directed to polynucleotides or polypeptides include a limitation relating to "hybridizing" to (the complement of) a VEGF-2 polynucleotide or portion of a VEGF-2 polynucleotide. (See, *e.g.* claims 16-20, 34-45, and other claims dependent therefrom.) However, the claim limitations directed to polynucleotide hybridization do not serve to distinguish the prior art that discloses VEGF, PlGF, or PDGF polynucleotides and/or polypeptides, because any DNA can hybridize to VEGF-2 DNA if the hybridization conditions (*e.g.* temperature and ionic strength) are sufficiently relaxed. Neither the claims nor the specification

require a level of hybridization stringency that would exclude VEGF, PIGF, or PDGF polynucleotides or encoded polypeptides from the scope of the claims. (No minimum level of hybridization stringency is required at all.)"

4.39 As I read the claims I do not read them as being directed to VEGF, PIGF, or PDGF. I believe the patent specification provides sufficient information and direction to a skilled reader to understand that the hybridization language used in the specification and recited in the claims do not include polynucleotides encoding VEGF, PIGF or PDGF. Given that there is no detectable homology at the nucleotide level between VEGF-2 and the other members of the PDGF/VEGF family, these sequences will not cross hybridize, particularly using the hybridization conditions recited in the claims. I refer to and repeat my comments in paragraphs 4.28 to 4.30 above, which addresses this matter in more detail.

Paragraph 2.7

4.40 In paragraph 2.7 Associate Professor Rogers refers to a number of publications, which he says teach the subject matter claimed in the patent specification. I have reviewed each of documents **D1, D5, D7, D12, D16, D18, D19, D20, D29, D34, D35, D36, D39** and **D41**. None of these documents describe VEGF-2. Further, to the extent that one or more of the claims in the patent specification might include a polypeptide that binds an antibody that binds to VEGF-2 I note that none of these publications describe an antibody that binds to VEGF-2 or establishes cross-reactivity between VEGF-2 antibodies and VEGF antibodies. These documents refer to such subject matter as VEGF, PDGF and PIGF. In my opinion they are not relevant to the subject matter claimed in the patent specification for the reasons mentioned in paragraphs 4.31 to 4.34, above.

Paragraph 2.7.2 (footnote)

4.41 In the footnote to paragraph 2.7.2 Associate Professor Rogers states:

> "...the opposed application only exemplifies an isolated cDNA, not an isolated VEGF-2 RNA or VEGF-2 genomic DNA."

4.42 However, at paragraph 3.4.3 Associate Professor Rogers states:

> "To the extent that the prior art had not explicitly isolated RNA or genomic DNA encoding any of these three polypeptides, it is my opinion that such RNA and genomic DNA was no more than routine variation over prior art disclosures of cDNAs..."

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4.43 The patent specification clearly identifies an isolated mRNA encoding VEGF-2. For example, Example 1 and Figures 4 and 5 of the patent specification teaches the isolation and detection of an mRNA species (see also the patent specification at page 27, lines 4 to 32). Furthermore, the isolation of VEGF-2 genomic DNA would have been a routine and straightforward task in 1994 for any person of ordinary skill in the field of molecular biology given the information in the patent specification.

4.44 Hence I would agree with Associate Professor Rogers' comments to the extent that they can be interpreted to mean that RNA and genomic DNA was a routine variation over the sequence information provided in the patent specification.

Paragraph 2.7.4

4.45 In paragraph 2.7.4 of Associate Professor Rogers' statutory declaration reference is made to a Response filed by HGS to the Australian Patent Office, which states: "biological activity may include immunogenic activity of the full length protein." (See Response paper dated 05 August 1998, filed by patent applicant.)". Associate Professor Rogers then states:

> "Immunogenicity is not generally considered to be a "biological activity" of a protein, because the term "biological activity" is generally used to describe the functions of a protein in native host cells or organisms where the protein does not normally cause an antibody response."

4.46 This is a specious statement. I would include immunological activity within the context of what is understood by the phrase biological function or activity. The ability of a protein to be able to bind an antibody regardless of its origin is, in my opinion, clearly a biological interaction and an activity that is dictated by the specific primary construction of the protein. Such activity is in my opinion a *bona fide* activity of a protein, since the antibodies may be used for clinical purposes, such as to inhibit a VEGF-2 mediated ailment or in a diagnostic manner such as to identify VEGF-2 activity. Thus immunological activity may be a biological function or activity that is dictated by the amino acid sequence of the identified protein.

4.47 Further, in paragraph 2.7.4 Associate Professor Rogers states:

> "...short peptide sequences of 5, 6, 7, or more residues could be considered biologically active fragments of VEGF-2, because fragments of this size are generally considered large enough to

elicit an immune response... Both VEGF-2 and the prior art human VEGF polypeptide contain an identical 7-mer sequence RCGGCCN... Thus, polynucleotides that encode VEGF satisfy the "encodes VEGF-2 or a biologically active fragment of VEGF-2" limitation of claims 13-15..."

4.48 At the conclusion of this paragraph Associate Professor Rogers identifies Documents D6 (p. 523 Fig. 1), D7 (p. 16319 Fig. 1), D12, D18 (p. 1307 Fig. 1A and 1B), and D34 to D36 as publications that anticipate claims 13 to 15. None of these documents establish that the amino acid sequence RCGGCCN preferentially binds a VEGF-2 antibody. Likewise document D29 (cited in footnote 8) which describes Balbiani Ring 3 Protein does not identify an antibody that preferentially binds VEGF-2 antibody. I refer to and repeat my comments in paragraphs 4.31 to 4.34, above.

Paragraph 2.7.5

4.49 In paragraph 2.7.5 Associate Professor Rogers states:

"Claims 16-18 are directed to an isolated polynucleotide which hybridizes to a VEGF-2 polynucleotide and which encodes a polypeptide which binds an antibody capable of binding to VEGF-2. As explained above in paragraphs 2.4-2.5, polynucleotides which encode VEGF satisfy the hybridizing limitation and encode a polypeptide (VEGF) which satisfies the antibody binding limitation."

4.50 I disagree. I refer to and repeat my comments in paragraphs 4.28 to 4.30, above, which address these matters in more detail.

Paragraph 2.7.12

4.51 In paragraph 2.7.12 Associate Professor Rogers states:

"As explained above in paragraphs 2.4-2.4.3, prior art polynucleotides that encode prior art VEGF polypeptides (or BR3P polypeptides) will hybridize to the VEGF-2 polynucleotides or fragments thereof recited in the claims. As explained in paragraphs 2.5 and 2.7.4, VEGF (and probably BR3P) polypeptides described in the prior art bind antibodies which bind to VEGF-2. Thus, VEGF polypeptides (and BR3P polypeptides) satisfy all of the limitations of claims 40-45, so these claims are anticipated by prior art documents that disclose VEGF (and BR3P) polypeptides."

4.52 In my opinion the conclusions reached by Associate Professor Rogers in this paragraph are not accurate. When I read the word "hybridize" in those claims I understand it to mean that the hybridization reaction

should be conducted under suitable conditions such as those described in Example 1 and stated on page 6, lines 2-5 of the specification. In Example 1, the patent specification teaches hybridization conditions that would not allow for cross hybridization of unrelated sequences, particularly VEGF or BR3P. These conditions are at either 65 degree C at 0.2xSSC or 60 degree C with 0.5XSSC and 0.1% SDS. Thus, the claims do not, in my opinion, encompass VEGF or BR3P polynucleotide sequences.

Paragraph 2.7.18

4.53 In paragraph 2.7.18 Associate Professor Rogers states:

> "...the claims directed to antagonists of VEGF-2 are not novel over prior art disclosures of forms of the receptors to which VEGF-2 could bind, but could not signal. See **Document D27** (disclosing a dominant negative Flk-1 protein)."

4.54 I can find no evidence in document D27 which establishes that the dominant negative Flk-1 protein described could bind VEGF-2. I observe that the dominant negative Flk-1 receptor described in D27 is created by deleting a significant portion of the intracellular kinase binding domain from part of one of the Flk-1 proteins that forms the receptor. Such a deletion may well inhibit binding of VEGF-2. In my opinion, no conclusions can be drawn from D27 about whether a dominant negative Flk-1 protein might serve as a VEGF-2 antagonist.

4.55 Separately claim 50 is directed to VEGF-2 antagonists. I note that that claim reads as follows

> "An antagonist specific for the polypeptide according to any one of claims 28 to 48"

4.56 I would understand the words "specific for" as used in this claim to mean that the antagonist must bind specifically to a VEGF-2 polypeptide and not one of the then known (i.e. in 1994) prior art polypeptides. Thus to the extent that Associate Professor Rogers refers to the Flk-1 receptor as a possible molecule that binds VEGF-2 I would note that it preferentially binds to VEGF and thus is not specific for VEGF-2. Hence I would not understand the Flk-1 receptor to fall within the scope of claim 50.

Paragraph 2.7.19

4.57 In paragraph 2.7.19 Associate Professor Rogers states:

> "...patients in need of VEGF-2 (or in need of inhibiting VEGF-2) would be treatable with VEGF (or with VEGF antagonists). Consequently, claims 51 and 52 embrace any prior art method of treatment of patients with VEGF polypeptides that are encompassed by claim 28 (or prior art method of treatment with VEGF antagonists)."

4.58 When I read the claims in the patent specification I note that they relate to a method of treating a patient in need of VEGF-2 using a VEGF-2 protein. I would not understand claims 51 to 52 to embrace a method of treating patients with VEGF, because the claims appear to me to be limited to the use of one or more VEGF-2 molecules.

Paragraph 2.7.21

4.59 In paragraph 2.7.21 Associate Professor Rogers states:

> "Since the Figures also disclose VEGF and PDGF's (See, *e.g.* Figures 2A-2B), I find that this reference to the Figures does not serve to exclude the prior art, and claims 57-61 are also anticipated."

4.60 I do not agree with Associate Professor Rogers' comments. I note that each of claims 57 to 61 are limited to earlier claims which specifically define VEGF-2 subject matter. In my opinion none of the identified claims encompass VEGF or PDGF. Hence I do not believe that the prior art molecules are covered by these claims.

Paragraph 3.4.2

4.61 In paragraph 3.4.2 Associate Professor Rogers states:

> "The specification also fails to provide any teaching or exemplification of active fragments, analogues, and/or derivatives of VEGF-2."

4.62 Separately, in paragraph 2.7.20 Associate Professor Rogers stated:

> "...the opposed application fails to identify with particularity any fragment, analogue, or derivative of the Figure 1 polypeptide which has an inhibitory activity."

4.63 I do not agree that the specification fails to describe fragments of VEGF-2. I refer to Example 2 in the patent specification where HGS describe a VEGF-2 fragment (see page 29 lines 17 to 24 of the patent specification).

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Further, at page 5 (lines 31 to 35) the patent specification describes two portions of VEGF-2, namely, the boxed area in Figure 2 which corresponds to amino acids 61 to 74 and the region bound by the cysteine residues which corresponds to amino acids 38 to 118.

4.64 Producing fragments, analogues or derivatives of a known sequence in 1994 was a routine task that I would expect any researcher of ordinary skill in the field of molecular biology would have been able to accomplish by employing standard and routine trial and experimentation. In this respect I refer to paragraph 3.2.5 of Associate Professor Rogers' Statutory Declaration where he makes the following comments:

> "The common general knowledge at the time of the filing of the priority application included knowledge of the following:
>
> .....
>
> materials and methods for generating short peptides of any desired amino acid sequence synthetically;
>
> materials and methods for selectively altering one or more codons of a gene and using the altered gene to produce proteins with one or more amino acids selectively changed or deleted or added;..."

4.65 Further, at paragraph 3.5 Associate Professor Rogers states:

> "Before the 1994 priority date, it was routine for the skilled addressee to introduce 3-4 amino acid (or codon) changes into a polypeptide (or polynucleotide) sequence, *e.g.* using procedures such as site-directed mutagenesis. [See, *e.g.* documents cited in paragraph 3.2.2, above.]."

4.66 These statements by Associate Professor Rogers are consistent with my comments about the routine nature of preparing VEGF-2 fragments, analogues or derivatives using the information in the patent specification.

4.67 Once an analogue fragment or derivative of VEGF-2 had been prepared it would then have been a matter of testing that molecule for the biological function or activity. Such activity could have been tested using any one or more of the *in vivo*, *in vitro* or immunological systems described in the patent specification. I refer to paragraphs 4.18 to 4.24 above which discuss the availability of such assays.

4.68 I believe the patent specification provides all of the information that I would have required to identify a fragment, analogue, or derivative of the Figure 1 polypeptide, which had an inhibitory activity. Likewise, the

patent specification contains all of the information that I would have required to produce active fragments, analogues, and/or derivatives of VEGF-2. I would not have needed (in 1994) examples in the patent specification before I could have produced or identified them and or tested them in a biological assay.

Paragraph 3.7.1

4.69 In paragraph 3.7.1 Associate Professor Rogers states:

> "I find no description of any instances where VEGF-2 gene therapy was successfully performed, or even attempted. Also, I find no teachings or guidance relating to performing gene therapy treatment that were not within the common general knowledge in Australia at the time of filing the opposed application."

4.70 The description of gene therapy provided in the patent specification is in my opinion suitably descriptive of the process involved. The success of such an approach would depend on the use of external technologies such as those used to deliver the VEGF-2 gene.

4.71 Had I wanted to identify publications describing gene therapy approaches as at March 1994 I would have conducted a Medline search. Some publications providing examples where gene therapy had been successfully used prior to March 1994 are illustrated below.

4.71.1 Stewart C, Taylor NA, Docherty K, Bailey CJ (1993) "Insulin delivery by somatic cell gene therapy." *J. Mol. Endocrinol.* 11:335-341.

4.71.2 Walsh CE, Liu JM, Miller JL, Nienhuis AW, Samulski RJ (1993) "Gene therapy for human hemoglobinopathies." *Proc. Soc. Exp. Biol. Med.* 204:289-300.

4.71.3 Kay MA, et al. (1993) "In vivo gene therapy of hemophilia B: sustained partial correction in factor IX-deficient dogs.". *Science* 262:117-119.

4.71.4 Kolodka TM, Finegold M, Kay MA, Woo SL (1993) "Hepatic gene therapy: efficient retroviral-mediated gene transfer into rat hepatocytes in vivo." . *Somat. Cell Mol. Genet.* 19:491-497.

4.71.5 Hyde SC, et al. (1993) "Correction of the ion transport defect in cystic fibrosis transgenic mice by gene therapy." *Nature* 362:250-255.

4.71.6 Goldspiel BR, Green L, Calis KA (1993) "Human gene therapy." *Clin. Pharm.* 12:488-505.

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4.72 Had I wanted to carryout VEGF-2 gene therapy I would have consulted both the description of gene therapy provided in the patent specification and one or more gene therapy publications, such as those list above.

4.73 Given the information in the patent specification and the state of the literature so far as it pertained to gene therapy by 1994 I believe that the description provided in the patent application is sufficient for me to perform experiments leading to gene therapy treatment.

Paragraph 4.6.4

4.74 In paragraph 4.6.4 Associate Professor Rogers states:

> "...the applicant and inventors failed to predict what appears to be one of the most important activities of VEGF2, that of a growth factor for the lymphatics system."

4.75 The patent specification states that VEGF-2 can be used in the promotion of endothelialization (see for example page 4 lines 11 and 12, page 17 and 18 of the patent specification). By 1994, the lymphatic system was known to be composed of endothelial cells. Moreover the intrinsic growth characteristics of lymphatic endothelium and vascular endothelium were reported to share similarities. Some publications reporting this knowledge are illustrated below:

4.75.1 Yong LC, Jones BE (1991) "A comparative study of cultured vascular and lymphatic endothelium" *Exp. Pathol.* 42:11-25; and

4.75.2 Witte MH, Witte CL (1987) "Lymphatics and blood vessels, lymphangiogenesis and hemangiogenesis: From cell biology to clinical medicine" *Lymphology* 20: 257-266.

Paragraph 4.7

4.76 In paragraph 4.7 Associate Professor Rogers states:

> "A molecular biologist would not have expected a partial eukaryotic polynucleotide sequence to be properly expressed in eukaryotic cells if the sequence were missing the first 69 codons."

4.77 Had I been presented with the patent specification at 1994 I would have attempted to produce the protein as described in the patent specification. In the process of attempting to do so, one of the options that I would have employed would have been to express the protein using a heterologous secretion signal sequence as described in the patent specification. If I

had thought that it was possible the sequence presented in the patent specification was in fact a truncated form of a larger molecule, I would have also attempted to clone more of the 5' end of the gene. Hence I would have followed the teachings in the patent specification and I would have looked further upstream for additional coding sequence for the full-length molecule.

4.78 In view of the above I do not agree with the comments of Associate Professor Rogers. I believe that using routine trial and experimentation a scientist of ordinary skill would have been able to produce the biologically active protein identified as VEGF-2 in the patent specification in eukaryotic cells even if the sequence were missing the first 69 codons.

Paragraph 4.8

4.79 In paragraph 4.8 Associate Professor Rogers states:

> "The failure to demonstrate a VEGF-2 activity and the failure to provide a VEGF-2 activity assay and the suggestion that VEGF-2 may have several activities (uses) place an undue burden on the part of the skilled addressee to practice the invention."

4.80 I disagree with this statement. In my opinion the patent specification provides sufficient information to permit a person of ordinary skill to practice the invention. I refer to and repeat paragraphs 4.18 to 4.24 above, which highlight some of the information provided in the patent specification.

Paragraph 4.10

4.81 In paragraph 4.10 Associate Professor Rogers refers to claims 16-27, 40-50 and 57-61 and suggests that the subject matter claimed in those claims was not intended by HGS to be part of the invention. I do not agree with that suggestion nor on my reading does the patent specification (see pages 4 and 22 to 24 where HGS provide a variety of suggested uses for which the defined fragments may be used).

4.82 Further, Associate Professor Rogers indicates there is no suggestion by HGS that antibodies had been made at the time the patent specification was filed. Regardless of whether HGS had actually produced any antibodies at the time of filing the patent specification, on page 23 there is a disclosure identifying how to produce such antibodies, which in my opinion any person of ordinary skill could have followed to generate

VEGF-2 antibodies. It was not necessary that the patent specification establish that HGS had made antibodies, before I could have taken the disclosed amino acid sequence and used it to generate such antibodies.

4.83 Associate Professor Rogers also suggests that HGS has not identified all of the antigenic sites on the VEGF-2 molecule. Although computer programs where readily available in 1994 to generate this information, I would not have needed such information. To determine whether a protein sequence would bind a VEGF-2 antibody is simply a matter of testing it. Additionally, as described in the specification, one routine way to generate antibodies is to inject isolated protein into a rabbit, which causes the rabbit to naturally raise antibodies against VEGF-2. In this method, it is not necessary to know the antigenic sites in order to generate the antibodies. Nothing further is required and any researcher in this field could have identified such binding.

Paragraph 4.13.1

4.84 In paragraph 4.13.1 Associate Professor Rogers states:

> "The opposed application reports that a message of 1.6 kD was observed in Northern hybridization studies. Initially, I note that scientists do not normally report the size of mRNA in kiloDaltons (kD, a measurement of molecular weight), but rather, report such sizes in length, *e.g.* kilobases (kb)."

4.85 From reading the patent specification it is clear to me that the reference to kD in Example 1 is a typographical error and should in fact be read as kb. No other possible explanation makes sense. This reasoning is also consistent with the information presented in Figure 5.

4.86 Further, in paragraph 4.13.1 Associate Professor Rogers states:

> "I observe that the description of the experimental results in the text of the specification does not correspond with the results depicted in the Figure. There is no significance whatsoever ascribed to the results allegedly depicted in Figure 5. Figure 5 appears to depict hybridization of a VEGF-2 probe to an mRNA species identified as 1.3 kb in size, which is inconsistent with results reported in Example 1 (Figure 4 and text) and inconsistent with other studies."

4.87 Figure 5 illustrates that VEGF-2 may be isolated from a range of different tissues.

4.88 Associate Professor Rogers comments on the band of mRNA species at 1.3kb. I would regard the VEGF-2 sequence identified in the patent specification that has a 1.6kb molecular weight to be within the range of error for the 1.3 kb band identified in Figure 5. Experiments of the nature presented in Example 1 and Figure 5 are not highly accurate. Further, strict alignment is not observed between the molecular weight markers and the molecular weight identification on the other side of the gel. Thus I do not believe that this result necessarily reflects that VEGF-2 was not isolated.

Paragraph 4.13.3

4.89 In paragraph 4.13.3 Associate Professor Rogers comments on Example 2. Before turning to Associate Professor Roger's comments I would like to make some observations about Example 2.

4.90 When I read Example 2 I noted that there are a number of errors in the Example that appear to me to be typographical in nature. First, Example 2 fails to identify the sequence of VEGF primer F5. I will discuss this issue in more detail below.

4.91 Second, Example 2 on page 29, line 21 refers to lanes 1 and 3, however this reference is inconsistent with the results presented in Figure 6. I believe the reference to lanes 1 and 3 should read lanes 3 and 5, which is consistent with the Figure 6 data. As reported in the legend associated with figure 6, lane 1 represents molecular weight markers. Thus lane 1 can not possibly represent a PCR product of full length VEGF-2 cDNA. Further the reference to lane 2 at line 24 should read lane 4. This would have been obvious to me and I believe a person of ordinary skill in my field, when regard is had to Figure 6.

4.92 Third, I note that the F4 primer is located about 119 bp away from the 3'end of the stop codon and about 242 bp before the last nucleotide of the cDNA. Further reference to the F4 primer should I believe be a reference to the F5 primer since it binds the VEGF sequence outside the VEGF-2 ORF. Thus the patent specification fails to provide the F4 primer. The specification states however that the F4 primer binds the nucleotide sequence approximately 36 amino acids before the COOH end of the VEGF-2 ORF. Since the specification provides the nucleotide sequence in this locality I and I believe any other researcher of ordinary skill in the field could have used Figure 1 to generate a suitable primer

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that would lead to the production of a VEGF-2 sequence truncated by 36 amino acids at its COOH terminus.

Paragraph 5.6

4.93 In paragraph 5.6 Associate Professor Rogers states:

> "Many of the claims (*e.g.*, at least claims 1-4, 11, 13-20, 28, 32, 34-45, and certain claims that depend therefrom) seek protection well beyond any consideration provided in the application to the extent that they can be interpreted to read on non-human forms of the VEGF-2 polynucleotide or polypeptide or uses thereof."

4.94 The patent specification teaches to me the existence of VEGF-2 generally and the information provided in the patent specification is sufficient, in my opinion, to identify and isolate VEGF-2 from other mammalian and animal species using standard and routine probing or PCR procedures that were commonly available in 1994. Hence I do not regard the patent specification to be limited to human VEGF-2. Any person of ordinary skill in the field could have used the information in the patent specification to produce probes and / or primers, which could have been used to identify VEGF-2 from another mammalian and animal species.

Paragraph 5.8

4.95 In paragraph 5.8 Associate Professor Rogers refers to a number of the claims in the patent specification that specifically define individual fragments of VEGF-2. I am aware that there is an error in the numbering of the amino acids in SEQ ID NO: 2. The amino acid sequence designated one (1) to five (5) (inclusive) actually constitutes amino acids one (1) through six (6) (inclusive). When this error is taken into account, all of the amino acid numbering appears to me to be correct.

Paragraph 5.8.1

4.96 In paragraph 5.8.1 Associate Professor Rogers comments on claims 11 and 32 in the patent specification. In that paragraph he states:

> "...it remains my opinion that the specification evinces no intent *to claim* a genus of polypeptides using this sequence as the critical, defining limitation. The context of the quoted statement indicates that the statement is merely one of comparison of the structural-relatedness of the VEGF-2 sequence to prior art sequences. There is no mention of the exact sequence *per se*, but rather, merely an observation that VEGF-2 includes a segment that

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matches a motif (PXCVXXXRCXGCCN, where X is any amino acid)."

4.97 I disagree with Professor Rogers where he suggests that there is no mention of the exact sequence *per se*. Immediately after the identification of the signature motif on page 5 of the patent specification there is a reference to Figure 2. In Figure 2 the signature motif is defined as a boxed region between amino acids 61 to 74, wherein the exact sequence of the signature motif is defined. Thus, in my view, the patent specification does define the signature motif.

4.98 I note that Associate Professor Rogers makes a comment that in his opinion there is no intention in the patent specification to claim polypeptide sequences with the signature motif as the limiting feature. The patent specification by way of the disclosure on page 5 and Figure 2 clearly identifies the signature motif. Further, the patent specification on page 9 makes clear to me that it includes fragments of VEGF-2. Given that the identified signature motif is conserved between VEGF family members I would have understood that the identified signature motif is one of the fragments that is talked about on page 9 of the specification. Thus the patent specification does support fragments bounded by amino acid residues 61 to 74.

Paragraphs 5.8.2 & 5.8.3

4.99 In paragraph 5.8.2 and 5.8.3 Associate Professor Rogers discusses claims 34 and 40. For similar reasons I believe the patent specification provides support for claims 11 and 32 I also believe that it provides support for claim 34 and 40. I refer to and repeat my comments in paragraphs 4.94 to 4.96, which address this matter.

Paragraph 5.8.4

4.100 In paragraph 5.8.4 Associate Professor Rogers refers to claims 12 and 33 and states:

> "There is only mention of the cysteines, and no mention of the intervening 70+ amino acids that are dispersed between the cysteines and that comprise most of the sequence between 37 and 117."

4.101 I do not agree with this statement. The patent specification on page five identifies the eight cysteine residues as being of importance in the overall structure of VEGF-2. Further SEQ ID No: 2 and Figure 1 identify each of

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the subject cysteine residues, including all of the intervening residues. I believe that all of the necessary information to produce this sequence as a fragment of VEGF-2 is provided in the patent specification. Moreover page 5 of the patent specification makes clear to me that HGS identified the sequence bound by amino acids 37 to 117 as being a significant portion of the disclosed VEGF-2 sequence.

Paragraphs 5.8.5 & 5.8.6

4.102 In paragraph 5.8.5 and 5.8.6 Associate Professor Rogers discusses claims 35 and 41. To the same extent that I consider the patent specification provides support for claims 12 and 33, it also provides support for claim 35 and 41. I refer to and repeat my comments in paragraphs 4.98 to 4.99, which address this matter.

Paragraph 5.8.10

4.103 In paragraph 5.8.10 Associate Professor Rogers refers to claim 39 and states:

> "As explained above in detail, Example 2, which provides the only arguable description of VEGF-2 mRNA, apparently was performed incorrectly, and VEGF-2 mRNA was misidentified .....Thus, I find no support in the application for this term, either."

4.104 I disagree. I refer to page 4 of the patent specification, which discloses RNA polynucleotides. Additional disclosures of such subject matter may be found on page 6 of the specification and in Example 1, where I note the applicant actually identified a number of VEGF-2 mRNA species. The probe that was used in the hybridization reaction described in Example 1 was a VEGF-2 sequence as disclosed in the patent specification. Having regard to the hybridization conditions used in Example 1 I believe that the results presented in Figure 5 support the identification of VEGF-2 mRNA, which therefore means that such mRNA can be isolated using routine and conventional PCR and cDNA techniques.

Paragraph 5.9

4.105 In paragraph 5.9 Associate Professor Rogers states:

> "When one considers what is now known about VEGF-2, it becomes apparent that the consideration provided in the specification is little more than a partial sequence with no demonstration of activity."

4.106 I disagree that the patent specification provides little more than a partial sequence with no demonstration of activity. In my opinion the patent specification provides all of the essential information required to identify and produce a biologically active VEGF-2 as well as guidance as to the uses of that protein. I refer to paragraphs 4.3 to 4.24 above which highlight the information contained in the patent specification.

Paragraph 6.6

4.107 In paragraph 6.6 Associate Professor Rogers states:

> "Because the definition of "activity" is unclear, the definitions of "antagonist" and "inhibitory activity" cannot be ascertained."

4.108 When I read the patent specification I note that it describes, for example, at least an activity of VEGF-2 as being an ability to proliferate endothelial cells. Other activities such as wound healing or as inhibitors of tumours, etc. are also discussed. Thus, I would understand an antagonist of VEGF-2 to be something that interferes with one or more of the biological activities of VEGF-2 as illustrated in the patent specification. Such terms were well known and well understood by researchers of ordinary skill in the field by 1994.

Paragraph 6.8.2

4.109 In paragraph 6.8.2 Associate Professor Rogers refers to claims 51 and 54 and states:

> "Claims 51 and 54 (and claims dependent therefrom) are ambiguous in that each apparently intends that a therapeutic amount of a polypeptide can be administered without administering any polypeptide whatsoever. In particular, claim 54 specifies that the therapeutically effective amount of polypeptide is administered by providing DNA to a patient. DNA is not a polypeptide, but a polynucleotide. Thus, even though claims 51 and 54 on their face recite administration of a polypeptide therapeutic, the applicant apparently intends for these claims to encompass gene therapy that does not involve administering *any* of the indicated polypeptide. Thus, the meaning of "therapeutically effective amount of the polypeptide" is unclear, and apparently includes an amount equal to zero."

4.110 When I read claims 51 and 54 I understand them to be referring to a method of treating a patient by administering to that patient a therapeutically effective amount of a VEGF-2 polypeptide. Two means are defined for administering the amino acid sequence. In the first

method (claim 51) the polypeptide is administered directly to the patient. In the second method (claim 54) the polypeptide is delivered via a process of DNA expression *in vivo*. In each instance the amount of protein that can be delivered to a patient can be controlled to give a specific therapeutic effect. The delivery of therapeutically effective amounts of a polypeptide can be empirically determined applying routine trial and experimentation.

4.111 When Associate Professor Rogers states: "...claim 54 specifies that the therapeutically effective amount of polypeptide is administered by providing DNA to a patient. DNA is not a polypeptide, but a polynucleotide...", I do not know what he means. As I read the claims I would not understand them to be suggesting that DNA is a polypeptide. In my opinion the claims require the administration of a DNA sequence in a manner permitting expression of a VEGF-2 polypeptide and nothing more.

4.112 In my opinion this subject matter is clearly supported by pages 18 and 19 in the patent specification. Moreover using the general information in the patent specification and nothing more than routine trial and experimentation a person of reasonable skill in the field could have practiced the method defined by claim 54.

AND I make this solemn declaration by virtue of the Statutory Declarations Act, 1959 and subject to the penalties provided by that Act for the making of false statements in statutory declarations, conscientiously believing the statements contained in this declaration to be true in every particular.

DATED this 12th day of December 2000.

DECLARED at: Brisbane, Queensland)

BEFORE me:.....)

.....

JOHN STANLEY MATTICK

K Brodenick (J.P.Qual)

.....

~~Commissioner of Declarations/Patent~~ Attorney/Justice of the Peace/~~Solicitor~~

Kellie Ann Brodenick
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BARDON QLD 4065

COMMONWEALTH OF AUSTRALIA

(Patents Act 1990)

IN THE MATTER OF: Australian Patent Application 696764 (73941/94). In the name of:
Human Genome Sciences Inc.

- and -

IN THE MATTER OF: Opposition thereto by Ludwig Institute for Cancer Research, under Section 59 of the Patents Act.

Annexure JSM-1

This is **Annexure JSM-1** referred to in my Statutory Declaration made this 12th day of DECEMBER 2000.

John Stanley Mattick

WITNESS: K. Broderick (J P Qual) 7707

~~Commissioner for Declarations/Solicitor~~
~~Patent Attorney~~/Justice of the Peace

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JOHN STANLEY MATTICK

Professor of Molecular Biology
Director, Australian Genome Research Facility
Director, Special Research Centre for Functional and Applied Genomics
Co-Director, Institute for Molecular Bioscience
The University of Queensland, Brisbane, Australia 4072

BIOGRAPHICAL SUMMARY

John Mattick was born in Sydney in 1950 and was educated at St Patrick's College, Strathfield, where he was Dux. He received his B.Sc with First Class Honours in Biochemistry from the University of Sydney in 1972, followed by a PhD in Biochemistry in 1977 from Monash University, on the topic of mitochondrial DNA replication and mutation. He then undertook postdoctoral work on the molecular biology of the fatty acid synthetase complex at the Baylor College of Medicine in Houston Texas from 1977 to 1981. His work on the architecture and function of this complex is now standard in biochemistry textbooks. He returned to Australia in early 1981 to work as a research scientist at the (then) CSIRO Division of Molecular Biology in Sydney, where he was the leader of a team responsible for the development of one of the world's first genetically engineered vaccines (against ovine footrot), for which he was awarded the 1989 Pharmacia-LKB Biotechnology Medal from the Australian Society for Biochemistry and Molecular Biology.

In 1988 he was appointed Professor of Molecular Biology and Foundation Director of the Centre for Molecular Biology and Biotechnology at the University of Queensland. The Centre was subsequently made a Special Research Centre of the Australian Research Council, and In 1994 was renamed the Centre for Molecular and Cellular Biology. The Centre has grown rapidly and has a strong national and international reputation for its research on the molecular biology of mammals and their diseases, including gene mapping, gene regulation, and developmental and cell biology. The Centre has over 140 staff and research students, and in 2000 was integrated into a new Institute for Molecular Bioscience (IMB), which is currently being constructed as part of a $110m research complex in conjunction with CSIRO. Professor Mattick is Co-Director of the IMB, and Director of a new ARC Special Research Centre for Functional and Applied Genomics, which was also established in 2000. Professor Mattick is also the Director of the Australian Genome Research Facility which was established under the Major National Research Facilities Program in 1987 with a $10m grant from the Australian Government, and which has its headquarters and DNA sequencing division at the University of Queensland, and its genotyping and mutation detection division at the Walter and Eliza Hall Institute of Medical Research in Melbourne.

Professor Mattick is an advocate of research into the information content of genes, including the Human Genome Project. He has worked in Sydney, Melbourne, Houston, Brisbane, Cambridge and Oxford, on viruses, bacteria and mammals, including protein chemistry, cell culture, and gene cloning and expression. His current research interests include the molecular genetics of host infection by type 4 fimbriate bacterial pathogens such as *Pseudomonas aeruginosa*, the analysis of the *P. aeruginosa* genome, the molecular biology of mammalian embryogenesis, and the role of introns and RNA processing in the evolution and development of multicellular organisms. He has advanced

the radical notion that introns and other so-called "junk" RNA molecules produced by the higher organisms represent a parallel processing system for gene control, the evolution of which was the critical step in the emergence 500 million years ago of sophisticated multicellular organisms from the unicellular life forms that had occupied the Earth's biosphere for the preceding 3 billion years. He has published over 100 papers in molecular biology, and was awarded the Eppendorf Achievement Award at the 2000 Lorne Genome Conference for his services to Australian Molecular Biology.

Professor Mattick has been a member of the Board of the Australian National Genome Information Service (ANGIS) since its inception in 1991. He is a member of the Human Genome Organisation (HUGO) and was the Chairman of the Organising Committee of the 1999 Human Genome Meeting (HGM'99) held in Brisbane, and a member of the Scientific Committees of the 1998 Human Genome Meeting (Turin) and the 2000 Human Genome Meeting (Vancouver). Since 1997 he has been a member of the Australian Health Ethics Committee and the Research Committee of the National Health and Medical Research Council, and over the past 12 years has served on numerous NHMRC Regional Grants Interviewing Committees and *ad hoc* Committees of Review for Program and Institutional Block Grants, as well as on the advisory boards of several organisations, including the Wellcome Trust Australian Medical Research Fellowships, the John Curtin School of Medical Research, the Mater Medical Research Institute and the Australian Proteome Analysis Facility. He is currently a member of the Executive of BIOCOG (Biotechnology Consultative Group) which advises the Federal Minister for Industry, Science and Resources, and is a member of the Queensland Biotechnology Advisory Council.

CURRICULUM VITAE

JOHN STANLEY MATTICK

PERSONAL

Date of Birth: 26th April, 1950
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Current Positions: Professor of Molecular Biology
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Director, Australian Genome Research Facility
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Family: Married to Louise Ellen O'Gorman
Three sons (John, born 1988; James, born 1997; Angus, born 2000)

DEGREES AND AWARDS

Undergraduate: B.Sc. (First Class Honours in Biochemistry) 1968-1971
The University of Sydney

Postgraduate: Ph.D. 1972-1977
"The replication and maintenance of mitochondrial DNA
in *Saccharomyces cerevisiae*"
Department of Biochemistry, Monash University

Postdoctoral Pharmacia-LKB Biotechnology Medal,
Australian Biochemical Society 1989

Butland Visiting Professorship, The University of Auckland 1997

Eppendorf Achievement Award, Lorne Genome Conference 2000

PROFESSIONAL HISTORY

1977-1981	Department of Biochemistry, Baylor College of Medicine Houston, Texas, U.S.A.
1977-1979	*Research Associate*
1979-1981	*Member of Faculty (Instructor)*

1982-1988	CSIRO Division of Molecular Biology, Sydney, NSW
1982-1984	*Research Scientist*
1984-1987	*Senior Research Scientist*
1987-1988	*Principal Research Scientist*

1988-present	The University of Queensland, Brisbane, QLD
1988-present	*Professor of Molecular Biology, Department of Biochemistry*
1988-1990	*Director, Centre for Molecular Biology and Biotechnology*
1991-1993	*Director, ARC Special Research Centre for Molecular Biology and Biotechnology*
1994-1999	*Director, ARC Special Research Centre for Molecular and Cellular Biology*
1996-present	*Director, Australian Genome Research Facility*
2000-present	*Director, ARC Special Research Centre for Functional and Applied Genomics*
2000-present	*Co-Director, Institute for Molecular Bioscience*

Sep 1993 - Mar 1994	Visiting Scientist, Department of Genetics, The University of Cambridge, Cambridge UK
Mar 2000 - Sep 2000	Visiting Senior Research Fellow, St. John's College, and Department of Anatomy and Human Genetics The University of Oxford, Oxford UK

CURRENT PROFESSIONAL ACTIVITIES – partial list

- Member, Research Committee of the National Health and Medical Research Council
- Member, Australian Health Ethics Committee of the National Health and Medical Research Council
- Member, BIOCOG (Biotechnology Consultative Group, reporting to the Federal Minister for Industry, Science and Resources)
- Member, Board of the Australian National Genome Information Service
- Member, Board of the Australian Proteome Analysis Facility
- Member, Board of the Mater Medical Research Institute
- Member, Research Advisory Board of the John Curtin School of Medical Research

- Member, Board of Genset Pacific Pty. Ltd. and Australian Genome Diagnostics Pty. Ltd.
- Member, International Molecular Biology Network (IMBN) Asia-Pacific
- Member, Queensland Biotechnology Advisory Council

CURRENT RESEARCH INTERESTS

- The molecular genetics of host colonisation by type 4 fimbriate bacterial pathogens
- Analysis of the *Pseudomonas aeruginosa* genome
- RNA-binding proteins and gene expression during mammalian development
- RNA-based gene regulation and the role of introns in multicellular development
- Genome sequencing and genome evolution as an information system

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4. **Mattick, J.S.** and Nagley, P. (1977). Comparative studies of the effects of acridines and other petite inducing drugs on the mitochondrial genome of *Saccharomyces cerevisiae*. *Molec. Gen. Genet.* **152**: 267-276.

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PATENTS

1. ***Antigenic Preparation***

   (Australian Patent No. 34979/84)
   Cloning and expression of *Bacteroides nodosus* fimbrial subunit genes in heterologous hosts as a basis for production of new vaccines against footrot.
   Inventors: **J.S. Mattick** and B.J. Anderson
   Filed: Australia and New Zealand 2-11-84.

2. ***Improved Antigenic Preparation***

(Australian Patent No. 50154/85; International PCT No. W086/02557)
Morphogenetic expression of fimbrial subunit genes in *Pseudomonas aeruginosa*, or other compatible hosts, as a basis for the production of fimbrial antigens for vaccines against footrot and other type 4 fimbriate pathogens.
Inventors: **J.S. Mattick**, B.J. Anderson and T.C. Elleman
Filed: Australia, U.S.A., Europe, South Africa and New Zealand 29-10-85.

3. ***Peptide Production by Protein Engineering***

(Australian Patent No. 17049/88; International PCT No. W088/08430)
Use of type 4 fimbrial subunits as a vehicle for the expression and export in recombinant bacterial cells of peptide sequences, such as the FMDV VP1 epitope 144-159, introduced by oligonucleotide-directed gene mutagenesis.
Inventors: **J.S. Mattick** and P.A. Jennings
Filed: Australia, U.S.A., Europe 27-4-87.

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45.* Kennedy, H.D., Wood, S.A. and **Mattick, J.S.** (1995) The family of genes controlling alternative splicing in mammals. The 8th International Congress on Isozymes - Gene Families: Structure, Function, Genetics and Evolution, Brisbane, Queensland.

46.* **Mattick, J.S.** (1995) A-Z is not enough: the molecular genetics of type 4 fimbriae in *Pseudomonas aeruginosa* and related pathogens. The 3rd Australian Conference on Molecular Analysis of Bacterial Pathogens, Marysville, Victoria.

47.* **Mattick, J.S.** (1995) Intron-exon structure and the evolution of parallel processing. Michael J. D. White Memorial Lecture, Genetics Society of Australia, Canberra, ACT.

48.* Alm, R.A. and **Mattick, J.S.** (1995) Genes involved in the biogenesis and function of type 4 fimbriae in *Pseudomonas aeruginosa*. Workshop on Type 4 pili - biogenesis, adhesins, protein export, and DNA import, Schloß Ringberg, Germany.

49.* **Mattick, J.S.** (1996) Genome research - the information superhighway of biotechnology. 10th International Biotechnology Symposium, Sydney, NSW. Abstract S6-5, p. 42.

50. Wood, S.A. and **Mattick, J.S.** (1996) Fam is a novel ubiquitin-specific protease expressed during postimplantation mouse development. Australian and New Zealand Society for Cell Biology Meeting, Brisbane.

51.* **Mattick, J.S.** (1996) Genome research and drug discovery. 2nd Australia-Japan Symposium on Drug Design and Development, Cairns, Queensland.

52.* **Mattick, J.S.** (1997) The Australian Genome Research Facility. 2nd International Strategy Meeting on Human Genome Sequencing, Hamilton, Bermuda.

53. Whitchurch, C.B., Darzins, A., Alm, R.A., Hobbs, M., Martin, P.R., Nourse, C.R., Watson, A. and **Mattick, J.S.** (1997) *Pseudomonas aeruginosa* genes *pilL*, *chpA* and *chpB* are necessary for type 4 fimbrial biosynthesis and twitching motility. 97th General Meeting of the American Society of Microbiology, Miami USA. Abstract D-41, p. 214.

54.* **Mattick, J.S.**, Whitchurch, C.B., Martin, P.R., Alm, R.A. and Hobbs, M. (1997) Regulatory pathways affecting the biogenesis and function of type 4 fimbriae in *Pseudomonas aeruginosa*. VI International Meeting on *Pseudomonas*: Molecular Biology and Biotechnology, Madrid, Spain.

55.* **Mattick, J.S.**, Alm, R., Whitchurch, C.B., Martin, R. and Hobbs, M. (1998) The molecular genetics of type 4 fimbriae in *Pseudomonas aeruginosa* and related bacterial pathogens. 9th National BiotechnologySeminar, Penang, Malaysia.

56. Comolli, J., Waite, L., Hauser, A., Whitchurch, C., **Mattick, J.** and Engel, J. (1998) Pilin function is necessary for *Pseudomonas aeruginosa* cytotoxicity and invasion of epithelial cells. 98th General Meeting of the American Society of Microbiology, Abstract B-81, p. 69.

57.* **Mattick, J.S.** (1998) Genomics in Australia. Conference on Biological Informatics, Australian Academy of Science, Canberra.

58.* **Mattick, J.S.** (1998) The implications of the human genome project for medicine and healthcare in the 21st century. Australian Pharmaceutical Manufacturers Association Conference, Canberra.

59.* **Mattick, J.S.** (1998) Genomics and genetics in drug discovery and drug delivery. Third Australia / Japan Symposium on Drug Design and Development, Tokushima, Japan.

60.* **Mattick, J.S.** (1998) Intron function and eukaryote evolution. Queenstown 1998 Molecular Biology Meeting, Queenstown, New Zealand.

61.* **Mattick, J.S.** (1998) Genomics and genetics - from bacteria to humans. Joint Meeting of the New Zealand Microbiology Society and The New Zealand Society for Biochemistry and Molecular Biology, Masterton, New Zealand.

62.* **Mattick, J.S.** (1998) Host colonisation by *Pseudomonas aeruginosa*. Joint Meeting of the New Zealand Microbiology Society and The New Zealand Society for Biochemistry and Molecular Biology, Masterton, New Zealand.

63.* Beatson, S.A., Whitchurch, C.B. and **Mattick, J.S.** (1998) Whole genome analysis of *Pseudomonas aeruginosa*: identification of novel genes and pathways. Joint Meeting of the New Zealand Microbiology Society and The New Zealand Society for Biochemistry and Molecular Biology, Masterton, New Zealand.

64. L. Croft, B. Huang, R. Blakeley, S. Beatson, C.B. Whitchurch and J.S. Mattick (1999) Annotation of the *Pseudomonas aeruginosa* PA01 genome. Human Genome Meeting 1999 (HGM'99), Brisbane.

65.* Croft, L., Whitchurch, C.B., Beatson, S., Blakeley, R., Huang, B. and **Mattick, J.S.** (1999) Exploring the *Pseudomonas aeruginosa* genome. Abstract S31. *Pseudomonas'99*: biotechnology and pathogenesis. American Society for Microbiology, Maui, Hawaii.

66.* Whitchurch, C.B., Young, M., Leech, A., Semmler, A. and **Mattick, J.S.** (1999) The molecular genetics of type 4 fimbriae and twitching motility in *Pseudomonas aeruginosa*. Abstract S41. *Pseudomonas'99*: biotechnology and pathogenesis. American Society for Microbiology, Maui, Hawaii.

67. Clark, F., Croft, L., Schandorff, S., Burrage, K. and Mattick, J.S. (1999) ISIS – the intron database: a glimpse of intron function. Abstract S-18-03. Combio '99 (43rd Annual Meeting of the Australian Society for Biochemistry and Molecular Biology, 18th Annual Meeting of the Australian and New Zealand Society for Plant and Developmental Biology, and the 39th annual Meeting of the Australian Society of Plant Physiologists), Gold Coast.

68. Croft, L., Beatson, S.A., Whitchurch, C.B., Blakeley, R., Huang, B. and **Mattick, J.S.** (1999) One approach to developing a bacterial genome database. Abstract S-25-02. Combio '99 (43rd Annual Meeting of the Australian Society for Biochemistry and Molecular Biology, 18th Annual Meeting of the Australian and New Zealand Society for Plant and Developmental Biology, and the 39th annual Meeting of the Australian Society of Plant Physiologists), Gold Coast.

69. Kennedy, H.D., French, J., Verhagen A. and **Mattick, J.S.** (1999) The *ras*-GTPase-activating protein SH3-domain-binding family of proteins (G3BPs): implications in *ras*-GAP^{120} signalling to RNA stability and cancer progression. Abstract S-33-03. Combio '99 (43rd Annual Meeting of the Australian Society for Biochemistry and Molecular Biology, 18th Annual Meeting of the Australian and New Zealand Society for Plant and Developmental Biology, and the 39th annual Meeting of the Australian Society of Plant Physiologists), Gold Coast.

70. Utama, B., Kennedy, H.D., Ru, K. and **Mattick, J.S.** (1999) Isolation and preliminary characterization of a novel nucleolar protein. Abstract P-W-51. Combio '99 (43rd Annual Meeting of the Australian Society for Biochemistry and Molecular Biology, 18th Annual Meeting of the Australian and New Zealand Society for Plant and Developmental Biology, and the 39th annual Meeting of the Australian Society of Plant Physiologists), Gold Coast.

71.* Croft, L., Whitchurch, C.B., Beatson, S., Blakeley, R., Huang, B. and **Mattick, J.S.** (1999) Exploring the *Pseudomonas aeruginosa* genome. Abstract OP-A28, p. 433. 11th National Biotechnology Seminar, Melaka, Malaysia.

72. Croft, L., Schandorff, S., Clark, F., Burrage, K., Arctander, P. and **Mattick, J.S.** (2000) ISIS, an intron information system, and the prevalence of alternative splicing in the human genome. Human Genome Meeting 2000 (HGM'2000), Vancouver, Canada.

73.* **Mattick, J.S.** (2000) After the human genome project: implications for medicine, healthcare and humanity in the 21st century. The 11th International Congress of Endocrinology, Sydney.

RECENT LECTURES / RESEARCH SEMINARS

1. *The new genetics and the story of life.* The Queensland Museum, 1991.
2. *The scientific and commercial implications of genome projects and genome analysis.* The 10th Australian Biotechnology Conference, Melbourne, February 1992.
3. *The significance of genome research.* International Genome Science Meeting, Adelaide, February 1992.
4. *Microbial genomes.* International Genome Science Meeting, Adelaide, February 1992.
5. *The new genetics and zoological conservation.* The Second Joint ARAZPA/ASZK Annual Zoological Conference, Currumbin Sanctuary, April 1992.
6. *Genome analysis - a paradigm shift in biological research.* The Campus Genetics Society, University of New South Wales, April 1992.
7. *The new genetics and the story of life.* The 1992 Butler Memorial Lecture, University of Queensland, September 1992.
8. *A genome approach to exploring biological systems.* Fairfield Hospital, Melbourne, July 1993.
9. *The molecular genetics of type 4 fimbriae in bacterial pathogens.* Department of Genetics, Cambridge University, Cambridge, September 1993.
10. *The Gene Library.* Department of Biochemistry and Molecular Biology, UMIST, Manchester, October 1993.
11. *Does one gene equal one protein?* Department of Genetics, Cambridge University, Cambridge, March 1994.
12. *Does one gene equal one protein: the significance of introns and RNA-based gene regulation in eukaryotic evolution.* Adelaide Children's Hospital, Adelaide, June 1994
13. *Does one gene equal one protein: the significance of introns and RNA-based gene regulation in eukaryotic evolution.* Childrens Medical Research Institute, Sydney, June 1994.
14. *Does one gene equal one protein: the significance of introns and RNA-based gene regulation in eukaryotic evolution.* Department of Biochemistry, University of Queensland, Brisbane, August 1994.
15. *Does one gene equal one protein: the significance of introns and RNA-based gene regulation in eukaryotic evolution.* Queensland Institute for Medical Research, Brisbane, August 1994.
16. *The new genetics?* Genetic Futures: the scientific, ethical, social, religious and environmental implications of genetic technology. Conference held by The Australian

Institute of Ethics and the Professions at St Johns College, the University of Queensland, September 1994.

17. *Biogenesis of type 4 fimbriae in Pseudomonas aeruginosa and related pathogens.* Department of Microbiology and Immunology, The University of Adelaide, Adelaide, October 1994

18. *Graduation Address* The University of New South Wales Faculties of Science and Medicine, Sydney, October 1994.

19. *Does one gene equal one protein: the role of introns in eukaryotic development.* The John Curtin School of Medical Research, Australian National University, Canberra, October 1994.

20. *The 1995 Colliver Lecture: The new genetics - implications for our future.* The Queensland Museum, Brisbane, June 1995.

21. *The biogenesis, function and regulation of type 4 fimbriae, and their relationship to other virulence factors in Pseudomonas aeruginosa.* Institute of Molecular Medicine, University of Oxford, Oxford, November 1995.

22. *The importance of genome research to medicine.* Australian Medical Students Association 1996 Meeting, Brisbane, June 1996.

23. *RNA signalling and processing in mammalian development.* The Institute for Reproduction and Development, Monash Medical Centre, July 1996.

24. *The impact of molecular genetics on the future of chemistry.* 14th International Conference on Chemical Education, Brisbane, July 1996.

25. *RNA signalling and processing in mammalian development.* Johnson and Johnson Research Centre, Sydney, August 1996.

26. *Genomes and development.* Faculty of Science, Queensland University of Technology, Brisbane, September 1996.

27. *The Australian Genome Research Facility.* Peter MacCallum Institute for Cancer Research, Melbourne, September 1996.

28. *The Australian Genome Research Facility.* Genetics, Cancer and Cardiovascular Disease Conference, Lorne, September 1996.

29. *The human genome project.* Royal Society of Queensland Special Symposium *on Exploring our genes and genetic heritage*, Brisbane, October 1996

30. *Understanding the human genome.* XIIIth Annual Royal North Shore Hospital/ University of Technology Sydney Scientific Research Meeting, Sydney, November 1996.

31. *The impact of genome projects on medical research and the future of medicine.* AWT Edwards Oration at the 35th National Scientific Conference of the Australian Society for Medical Research, Gold Coast, November 1996.

32. *The information age in biotechnology.* The Licensed Executives Society (Australia and New Zealand), Brisbane, March 1997.

33. *Butland Visiting Professor Oration: The human genome project and the future of medicine.* The University of Auckland, Auckland, August 1997.

34. *RNA-mediated gene regulation in mammalian development.* Faculty of Health Sciences, University of Auckland, Auckland, August 1997.

35. *Type 4 fimbriae*. Faculty of Health Sciences, University of Auckland, Auckland, August 1997.

36. *The human genome project and the changing face of biology.* CONSTAQ '97 (1997 Conference of the Science Teachers Association of Queensland), Brisbane, August 1997.

37. *The human genome project and the future of biology.* The Leo Howard Vacation School, University of Queensland, Brisbane, January 1998.

38. *The impact of genomics on the future of biology and medicine. Human Genome Research - Science and Society.* The Garvan Institute of Medical Research, Sydney, April 1998.

39. *Genomics and biotechnology.* NZ Medical Research Council Foresight Meeting, Auckland, June 1998.

40. *Genomics in Australia.* Bioinformatics Conference, Australian Academy of Science, Canberra, July 1998.

41. *The Institute of Molecular bioscience.* University of Queensland Customs House, Brisbane, November 1998.

42. *Genomics.* 9th Wheat Breeding Assembly, Toowoomba, September 1999.

43. *The impact of genomics on the future of medicine.* Australian College of Legal Medicine, Canberra, October 1999.

44. *Novel therapies for the new millenium.* Leukaemia Foundation Annual Conference, QIMR, Brisbane, October, 1999.

45. *Genomics.* Biofutures Conference, The Brisbane Institute, Brisbane, October 1999.

46. *Host colonisation by Pseudomonas aeruginosa – complex signal transduction pathways which integrate multiple virulence factors and colonial behaviour.* Children's Medical Research Institute, Westmead, Sydney, October 1999.

47. *The end of reductionist biology.* The Queensland Protein Group, Brisbane, November 1999.

48. *Twitching motility in bacteria.* Department of Plant Sciences, The University of Oxford UK, May 2000.

49. *The molecular genetics of type IV pili and host colonisation in Pseudomonas aeruginosa.* Department of Cell and Molecular Biology, Umeå University, Umeå Sweden, June 2000.

50. *The role of introns and RNA-based gene regulation in eukaryotic evolution and development.* Department of Human Anatomy and Genetics, The University of Oxford UK, June 2000.

51. *The development of the Institute for Molecular Biosciences and the future of biology as an information science.* School of Biomedical Sciences, University of Ulster, Coleraine UK, June 2000.

52. *The molecular genetics of type IV fimbriae and host colonisation in Pseudomonas aeruginosa and construction of an interactive web-based genome database.* Department of Microbiology and Immunobiology, Queens University, Belfast UK, June 2000.

53. *The implications of the human genome project for medicine, healthcare and humanity in the 21st century.* The Kuringai District Medical Association and South African Medical Association, Sun City, South Africa, July 2000.

54. *Striking the balance in Australia: "A Code of Ethical Practice for Biotechnology".* Australian Biotechnology Event, World Expo 2000, Hannover, Germany, July 2000.

55. *Biomedical. Biotechnology and Pharmaceutical Innovation: Australia's Opportunities.* Australian Biotechnology Event, World Expo 2000, Hannover, Germany, July 2000.

56. *The role of introns and RNA-based gene regulation in eukaryotic evolution and development.* EMBL (European Molecular Biology Laboratory), Heidelberg, Germany, July 2000.

57. *The molecular genetics of type IV fimbriae and host colonisation in Pseudomonas aeruginosa and construction of an interactive web-based genome database.* Department of Medical Microbiology, St Bartholomew's and the Royal London School of Medicine and Dentistry, London, UK, July 2000.

58. *The molecular genetics of type IV fimbriae and host colonisation in Pseudomonas aeruginosa and construction of an interactive web-based genome database.* Lehrstuhl Biologie der Mikroorganismen, Ruhr-Universitaet Bochum, Bochum, Germany, September 2000.

59. *The molecular genetics of type IV fimbriae and host colonisation in Pseudomonas aeruginosa and construction of an interactive web-based genome database.* Institute for Molecular Medicine, Oxford, UK, September 2000.

60. *The evolution of controlled multitasked networks: a role for introns and other noncoding RNAs.* CNRS Marseille, France, September 2000.

61. *The molecular genetics and genomics of Pseudomonas aeruginosa host colonisation and pathogenesis.* Austin Research Institute, Melbourne, November 2000.

62. *The modern RNA world: tips of an iceberg.* Ludwig Institute for Cancer Research, Melbourne, November 2000.

SCIENTIFIC AND ACADEMIC SERVICES

Scientific Journals:

- Infection and Immunity - Reviewer
- Gene - Reviewer
- Molecular Microbiology – Reviewer
- Microbiology
- Journal of Bacteriology - Reviewer
- FEMS Microbiology Reviews – Reviewer
- Australian Medical Journal - Reviewer
- Asia-Pacific Journal of Molecular Biology and Biotechnology - Editorial Board

The University of Queensland

- Member, Academic Board 1989-present
- Member, Faculty of Science 1989-1996
- Member of the Executive, Faculty of Chemical and Biological Sciences 1997-present
- Member, Faculty of Medicine / Health Sciences 1990-1996

Other Institutions

- Member, NHMRC Regional Grants Interviewing Committee 1988-92, 1994,1998
- Chairman, NHMRC Regional Grants Interviewing Committee 1992, 1994, 1998
- Member, NHMRC Assigners Panel 1990-95
- Member, NHMRC C.J.Martin Fellowships Referee Panel 1990
- Member, Australian Wool Corporation Genetic Projects Review Group 1990
- Member, Selection Committee for the Australian National Genome Information Service 1990
- Member, NHMRC Fogarty Fellowships Committee 1991-92
- Member, Executive and Board of the Australian Genome Information Centre 1991-present
- Member, Biomedicine Advisory Board of the Australian Nuclear Science and Technology Organisation 1991-1994
- Member of Organizing Committee, the Xth Australian Biotechnology Conference, Gold Coast, Queensland, 1991
- Organizer/Convener, the 14th Annual Conference on the Organization and Expression of the Genome, Lorne, Victoria, 1992
- Foundation Director, Lorne Genome Conference Inc. 1992-1997
- Member, Review Committee of the Molecular Parasitology Program, CSIRO Division of Tropical Animal Production 1992
- Member, Quinquennial Review Committee of the Garvan Institute for Medical Research 1992
- Member, Hamilton NHMRC Program Grant Review Committee 1992
- Member, NHMRC Genome Working Party 1991-93
- Chair, NHMRC Genome Working Party 1994-96
- Member, Martin NHMRC Program Grant Review Committee, 1995
- Member, Joint Review of the John Curtin School of Medical Research, The Australian National University, 1995
- Member of Organizing Committee, the 8th International Conference on Isozymes - Gene Families: Structure, Function, Genetics and Evolution. Brisbane, Queensland, 1995
- Member of International Advisory Committee, the 10th International Biotechnology Symposium. Sydney, New South Wales, 1996
- Member of Council, Royal Society of Queensland, 1996-1997
- Member, Scientific Advisory Committee, Cooperative Research Centre for Vaccine Technology, 1996-1997
- Organizer/Convener, the 19th Annual Conference on the Organization and Expression of the Genome, Lorne, Victoria, 1997
- Member, Review Committee of Research at the Royal Adelaide Hospital, IMVS and the Hanson Centre, 1997
- Member, Board of Pacific Oligos Pty. Ltd., 1997-1999

- Member, Advisory Board of the John Curtin School for Medical Research, The Australian National University, 1997-2000
- Member, Board of the Cooperative Research Centre for The Discovery of Genes for Common Human Diseases, 1997-1999
- Member, Research Committee of the National Health and Medical Research Council, 1997-2003
- Member, NHMRC Australian Health Ethics Committee, 1997-2003
- Member, Research Review Committee of The Prince Charles Hospital, Brisbane, 1998
- Foundation Member. Asia-Pacific International Molecular Biology Network (IMBN), 1998 - present
- Member, Organising Committee of HGM'98 (Human Genome Meeting), Turin 1998
- Chair, Organising Committee of HGM'99 (Human Genome Meeting), Brisbane 1999
- Chair, Initial Quinquennial Review of the Victor Chang Heart Research Institute, 1999
- Member, Organising Committee, IXth International Congress of Bacteriology and Applied Microbiology, Sydney, 1999
- Member, Board of the Mater Medical Research Institute, 1999 - present
- Member, Program Committee ASM Pseudomonas '99 Conference, Maui, Hawaii, 1999
- Member, Board of the Australian Proteome Analysis Facility, 1999 – present
- Member, Advisory Panel. Universiti Kebangsaan Malaysia – Malaysia Technology Development Corporation (UKM-MTDC) Biotechnology Academy, 1999 – present
- Co-Editor (with Prof. Paul Davies), Frontiers of Science series (Allen & Unwin), 1999 - present
- Member, Scientific Advisory Board, Medica Holdings Pty. Ltd., 1999 – present
- Member, Executive of Biotechnology Consultative Group (BIOCOG), 1999 – present
- Member, Organising Committee of HGM'2000 (Human Genome Meeting) Vancouver, 2000
- Member, Board of Pacific Oligos Pty. Ltd., 2000 – present
- Member, Board of Australian Genome Diagnostics Pty. Ltd., 2000 – present
- Member, Scientific Advisory Committee of the Clive and Vera Ramaciotti Centre for Gene Function Analysis, University of New South Wales, 2000 – present
- Member, Queensland Biotechnology Advisory Council, 2000 - present

MEMBERSHIP OF PROFESSIONAL SOCIETIES

- The Australian Society for Biochemistry and Molecular Biology
- The Australian Society for Microbiology
- The Genetics Society of Australia
- The Lorne Genome Conference

COMMONWEALTH OF AUSTRALIA

(Patents Act 1990)

IN THE MATTER OF: Australian Patent Application 696764 (73941/94). In the name of:
Human Genome Sciences Inc.

- and -

IN THE MATTER OF: Opposition thereto by Ludwig Institute for Cancer Research, under Section 59 of the Patents Act.

Annexure JSM-2

This is **Annexure JSM-2** referred to in my Statutory Declaration made this 12th day of DECEMBER 2000.

John Stanley Mattick

WITNESS: K Brodrick (J.P. Qual) 7707

~~Commissioner for Declarations/Solicitor~~
~~Patent Attorney~~/Justice of the Peace

Kellie Ann Brodrick
143 Forrester Tce
BARTON QLD 4065

Summary Research History

John Stanley MATTICK

1.1 My training in molecular biology and biochemistry began in 1968 when I undertook an honours degree in science at the University of Sydney, Australia. My honours thesis investigated the control of cyclopropane fatty acid synthesis in *Pseudomonas denitrificans*.

1.2 After receiving a first class honours degree in 1972, I moved to the Department of Biochemistry at Monash University in Melbourne, Australia to undertake Ph.D. studies on the replication and maintenance of mitochondrial DNA in *Saccharomyces cerevisiae* (baker's or brewer's yeast, which is widely studied as a genetic model for cellular function). Between 1972 and 1977, I investigated replicative DNA synthesis in *Saccharomyces cerivisiae* mitochondria (see publications 2 and 3) and the effects of inhibitors and mutagens, such as ethidium bromide, acridines and their derivatives, on the replication and maintenance of the mitochondrial genome (see publications 1, 4, 5 and 6). In 1977, I received a Ph.D. for my research from Monash University.

1.3 In 1977, I moved to the United States of America to work as a Post-Doctoral Fellow in the Department of Biochemistry at Baylor College of Medicine in Houston, Texas. In the 1970s and early 1980s, Baylor College of Medicine was one of the leading centres for molecular biology in the world, and remains so today. At Baylor my research interests took on a new focus: an examination of the fatty acid synthetase complex, which is the enzyme system used to synthesise fats for membranes and for energy storage. Using molecular biology techniques, my colleagues and I isolated and cloned, for the first time, the fatty acid synthetase gene complex from yeast (see publication 11). I also purified messenger RNA (mRNA) encoding the corresponding mammalian and avian enzyme complexes (see publications 7 and 8) and developed a new system for the *in vitro* translation of mRNA into protein (see publication 10).

1.4 I also made monoclonal antibodies against the fatty acid synthetase complex and used these and other reagents, in conjunction with controlled proteolysis, to dissect its structure and architecture and to map the location of its active sites. This research was published in four consecutive papers in the Journal of Biological Chemistry (see publications 12, 13, 14 and 15) and provided a clear insight into the

mechanism by which the fatty acid synthetase protein complex works in animals, which is now the standard treatment in major biochemistry textbooks. We showed that fatty acid synthetase is a multi-enzyme complex that consists of a head-to-tail dimer of two identical polypeptide chains, which are encoded by a single gene. Each polypeptide chain is multi-functional in activity and contains all seven enzymatic functions and the acyl carrier required to synthesise lipids from 2-carbon compounds. This research provided me with experience in many of the techniques associated with gene cloning and expression including RNA isolation, mRNA purification, *in vitro* translation, cDNA synthesis, recombinant library construction and methods for screening recombinant libraries.

1.5 In 1981, I returned to Australia to take up a position as a Research Scientist with the (then) Commonwealth Scientific and Industrial Research Organisation ("CSIRO") Division of Molecular Biology in Sydney. CSIRO was interested in using my expertise to develop new recombinant DNA-based vaccines against important pathogens. At their request, I began by investigating the prospects for developing a vaccine against the blood-borne protozoan parasite *Babesia bovis* (which is related to malaria) (see publication 16), but the immunological basis for such a vaccine was unclear and this research was discontinued. During this time, however, I was also involved in the successful cloning, sequencing and identification by translation of hybrid-selected mRNAs of the cDNA sequences encoding the type-specific surface glycoprotein of rotavirus (which causes diarrhoeal disease) (see publications 17 and 18).

1.6 In 1983, I started working on the development of a recombinant DNA-derived vaccine against the bacterium *Bacteroides (*now *Dichelobacter) nodosus*, which causes footrot in ruminants, and for which the important protective antigens (called type 4 fimbriae) were known. I achieved this objective by isolating and cloning the gene sequences encoding these antigens from *Bacteroides nodosus*, expressing the corresponding proteins from those sequences and finally testing the proteins for their efficacy as a vaccine. The initial gene cloning component of my research was completed by the end of 1984, and the selection of a suitable bacterial host cell (*Pseudomonas aeruginosa*) to obtain correct folding and secretion of the protein, selection of a suitable expression vector and testing of a prototype vaccine, was completed by the end of 1985 (see publications 19, 20, 22, 30 and 33, and patents 1 and 2). This

represented the first successful genetically-engineered vaccine in Australia and one of the first in the world. For this work the Australian Biochemical Society subsequently awarded me the 1989 Pharmacia-LKB Biotechnology Medal.

1.7 During this time also, my (then) wife was concurrently employed as a Research Scientist at Biotech Australia Pty. Ltd. and was the leader of the successful project to clone and express human plasminogen activator inhibitor type 2, by constructing cDNA libraries and screening with oligonucleotide probes derived from partial amino acid sequence information. I closely followed and was familiar with her work on this project.

1.8 By about the end of 1985, I supervised a team of about 10 researchers, including a Post-Doctoral Fellow, Ph.D. students, CSIRO research assistants, and seconded employees of collaborating vaccine and biotechnology companies.

1.9 Between 1985 and 1988, my colleagues and I cloned the genes encoding related antigens from other *Bacteroides nodosus* serotypes to expand the range of coverage of the vaccine, and to improve the host-vector expression system to enable stable high-level production of these proteins for vaccine manufacture. This required optimisation of the promoter system to drive high level expression of the recombinant protein, selection of suitable vector systems that were stable in the host cell during large-scale fermentation, suitable splice sites for insertion of the cloned gene into the expression vector, and appropriate procedures for purification of the protein from recombinant culture (see publications 23, 24, 25, 26, 27, 29, 31, 32, 37, 42, 45, 46 and 56).

1.10 My team also examined other antigenic proteins and showed that the recombinant fimbrial expression system could be successfully used to manufacture vaccines against other bacterial pathogens, such as *Moraxella bovis* (which causes severe conjunctivitis and eye damage in cattle), and to produce antigenic epitopes from other organisms such as foot-and-mouth disease virus by site directed mutagenesis and protein engineering (see publications 36 and 41).

1.11 During this period I also worked as a consultant for the Mauri Foods Pty Ltd yeast genetic engineering program. I was also involved, then and

later, in the characterisation of important genes and proteins from bovine herpes viruses and enteroviruses (see publications 34, 43, 44, 63, 66 and 91).

1.12 In 1988, I was appointed the Foundation Professor of Molecular Biology and the Foundation Director of the Centre for Molecular Biology and Biotechnology ("the Centre") at the University of Queensland, positions that I continue to hold. I established and built the Centre and in 1990 it was designated a Special Research Centre of the Australian Research Council (formerly known as Commonwealth Centres of Excellence), one of only about twenty in all areas of science and one of only four in biology. The Centre was re-named the ARC Special Research Centre for Molecular and Cellular Biology in 1994. It specialises in the molecular genetics, developmental biology and cellular biology of mammals and their pathogens, and currently has over 130 staff and research students with an annual budget of around $7 million.

1.13 The laboratories in the Centre, including my own, routinely use recombinant expression systems in bacteria, yeast, insect cells (baculovirus) and animal cells to produce recombinant proteins for purposes such as x-ray crystallography and other forms of structural analysis, to generate antibody probes for various experimental purposes, and to study the biochemistry and interactions of such proteins with other proteins, RNA and DNA.

1.14 Since 1988, my research has focussed primarily on the molecular genetics of the biogenesis and function of type 4 fimbriae in a number of pathogenic bacteria, but particularly in *Pseudomonas aeruginosa* (which causes opportunistic infections in immuno-compromised individuals such as those suffering from cystic fibrosis, AIDS, burns and cancer chemotherapy) (see publications 28, 31, 35, 40, 46, 47, 51, 61, 62, 64, 65, 68, 69, 71, 72, 74, 75, 76, 77, 79, 81, 82, 83, 84, 85, 86, 87, 94, 95, 98, and 100).

1.15 I have also developed a program to identify genes involved in mammalian development and the role of RNA in this process (see publications 73, 78, 88, 89, 90, 92, 97, 99, 101, 102), as well as a number of new techniques in molecular biology (see publications 49, 60 and 67), and collaborative projects in mammalian gene cloning and mapping (see publications 48, 54, and 57). This involved, among other things, gene identification,

bioinformatic analysis and gene expression in heterologous expression systems to obtain antibodies to analyse functional roles of the encoded proteins *in vivo*. My colleagues and I have also been involved in various collaborative projects in gene expression and protein engineering. This has involved cloning of bacterial and mammalian genes, site-directed mutagenesis to alter the coding sequence and consequently the protein product, expression of the product and functional assays (see publications 52, 53, 58, 59, 88, and 101). My laboratory has also developed new vector systems for gene cloning and recombinant expression in bacterial cells (see publication 79). I have also been an active proponent of genome research in Australia (see publications 38, 39, 55, 70, 80 and 93).

COMMONWEALTH OF AUSTRALIA

(Patents Act 1990)

IN THE MATTER OF: Australian Patent Application 696764 (73941/94). In the name of:
Human Genome Sciences Inc.

- and -

IN THE MATTER OF: Opposition thereto by Ludwig Institute for Cancer Research, under Section 59 of the Patents Act.

Annexure JSM-3

This is **Annexure JSM-3** referred to in my Statutory Declaration made this 12th day of DECEMBER 2000.

J. J. Mattick

John Stanley Mattick

WITNESS: K. Broderick (J.P. Qual.) 77707

~~Commissioner for Declarations/Solicitor~~
~~Patent Attorney/~~Justice of the Peace

Kellie Ann Broderick
1/43 Forrester Tce
BARTON QLD 4065

COMMONWEALTH OF AUSTRALIA

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IN THE MATTER OF: Australian Patent Application 696764 (73941/94). In the name of: Human Genome Sciences Inc.

- and -

IN THE MATTER OF: Opposition thereto by Ludwig Institute for Cancer Research, under Section 59 of the Patents Act.

DOCUMENT LIST

Documents provided to me by the Patent Attorneys representing HGS in the subject proceedings are as follows:

1. Passaniti A, et al. (1992) *Lab. Invest.* 67:519-528.
2. Splawinski J, et al (1988) *Methods Find Exp. Clin. Pharmacol.* 10:221-226.
3. Andersson et al. (1992) *J. Biol. Chem.* 267:11260-11266.
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COMMONWEALTH OF AUSTRALIA

(Patents Act 1990)

IN THE MATTER OF: Australian Patent Application 696764 (73941/94). In the name of:
Human Genome Sciences Inc.

- and -

IN THE MATTER OF: Opposition thereto by Ludwig Institute for Cancer Research, under Section 59 of the Patents Act.

Annexure JSM-4

This is **Annexure JSM-4** referred to in my Statutory Declaration made this 12th day of DECEMBER 2000.

John Stanley Mattick

WITNESS: K. Broderick (J.P. Qual) 7727

~~Commissioner for Declarations/Solicitor~~
~~Patent Attorney/~~Justice of the Peace
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Table 1

Australian Patent Application 696764 (73941/94)

In the name of: Human Genome Sciences Inc.